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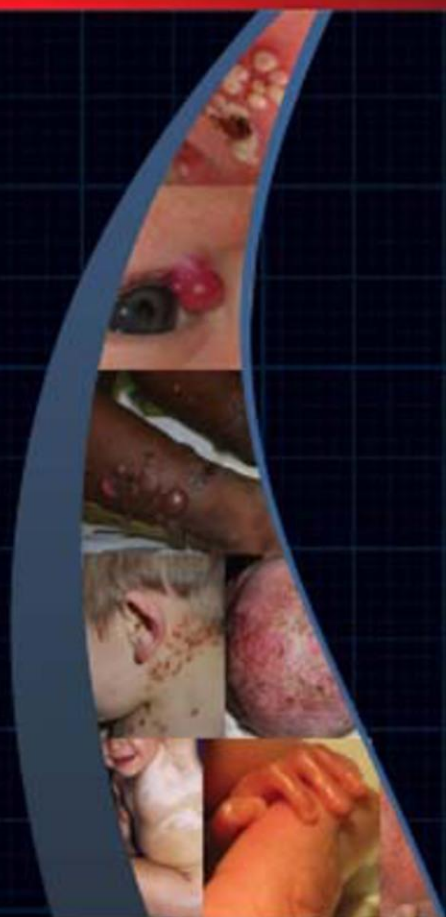
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Neonatal and Infant Dermatology

THIRD EDITION

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Neonatal and Infant Dermatology

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Third Edition

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Beginning in the late 1970s, the survival of infants born before 28 weeks' gestation began to improve. With enhanced survival, however, new challenges arose especially with regard to fluid and electrolyte homeostasis. It became clear that the skin of the preterm neonate was thin and permeable, greatly increasing insensible water loss. Neonatal care in the 1980s and 1990s was focused on ways to enhance skin integrity by applying ointments and vegetable oils to the skin and by altering environmental humidity to decrease insensible water loss. The widespread use of antenatal steroids, with their skin-maturing effects, further enhanced the ability of clinicians to regulate fluid and electrolyte balance.

At the beginning of this millennium, the focus of many NICUs shifted to prevention of healthcare-associated infections. Epidemiological studies demonstrated that even seemingly 'trivial' infections with low-grade pathogens such as *Staphylococcus epidermidis* were associated with an increase in neonatal morbidity and mortality rates. Once again the interest of clinicians and investigators was piqued as they identified the skin as a portal for infection, a site of transmission of infectious agents from one infant to another, and a first line of host defense. Bundled interventions, which emphasized careful attention to hand hygiene and maintenance of skin integrity, led to a significant reduction in the incidence of healthcare-associated infections.

We are now at the beginning of a new era focused on the physiology, biochemistry and host defense functions of newborn infant skin. No longer is the skin viewed as a passive barrier. The skin has all the elements of a functional hypothalamic, pituitary adrenal axis, producing cortisol and corticotropin-releasing hormone. Similar to the mucosal surfaces of the intestine and lung, the skin provides a complex system of immunoreactive cells and biologically active substances. Furthermore,

there is continuous trafficking of immune cells between the skin and regional lymphoid tissue and crosstalk between microbes colonizing the skin and immune cells. Keratinocytes in the skin have toll-like receptors, which allow recognition of molecular patterns on a wide variety of pathogens. They are also capable of producing antimicrobial peptides and cytokines. Even in preterm neonates, the skin is capable of well-developed inflammatory responses, limiting damage from pathogens, toxins and trauma and promoting wound healing. However, the skin of the preterm infant is slow to mature both as a barrier and organ of innate immunity. Enhancing the local immunity and barrier function of the skin (e.g. application of vernix caseosa) may be a potential strategy to decrease the risk of infection in the preterm population.

In the third edition of this textbook (previously edited by Solomon and Esterly) the editors, Eichenfield, Frieden, Mathes and Zaenglein, have expanded its scope to include skin disorders arising in the neonatal period and infancy. The wonderful aspects of the prior editions have been preserved or improved upon. The text is clearly written and enhanced by the many color photographs of dermatologic disorders. Whenever possible there is a renewed effort to include evidence-based recommendations. The genetic basis for many of the skin disorders is now known, and up-to-date information on the developmental differences in term and preterm infant skin has been expanded. *Neonatal and Infant Dermatology* is far more than an atlas. It is a state-of-the-art presentation of the diagnosis and management of skin disorders, and a road map for future interventions to enhance the well-being of the newborn infant.

Richard A. Polin MD

2014

PREFACE

We began this, the third edition of this textbook with the intention of a minor change in title and an expansion of the scope of the book. Over time we found ourselves turning to this book, not only as a reference when evaluating newborns with skin diseases, but infants as well. Hence the changed title to *Neonatal and Infant Dermatology*, 3rd edition. This has resulted in the addition of a few new chapters, the augmenting of others, as well as an overall updating of the entire book. We are very fortunate to have as co-editors two extremely able pediatric dermatologists, Erin Mathes and Andrea Zaenglein, who embraced the vision we had for the book, and helped immeasurably in

bringing it to print. We also thank the chapter authors for their outstanding contributions – without them the book would not exist. We hope the readers will agree with us that this is a textbook which you can turn to again and again as you see young infants with a wide variety of skin diseases.

Lawrence F. Eichenfield

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May 2014

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This book is dedicated to Nancy B. Esterly MD, mother of pediatric dermatology, consummate editor, and role model. Without her, this edition – as with the previous editions she contributed to as an editor – would not be possible.

Her intellect, sensibility, and love for pediatric dermatology continue to inspire us.

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Fetal Skin Development

STEVEN B. HOATH | THEODORA MAURO

Introduction

The skin simultaneously contacts a changing environment and provides closure for the body. It is a cellular and molecular interface, which plays a critical functional role in neurobehavior and perception.¹ The skin is embryologically continuous with the nervous system via involution and with the amnion via simple lateral extension. Thus, with regard to the fetoplacental unit, the skin is an ‘internal’ organ marking the boundary between the developing nervous system and the fetal membranes surrounding the liquor amnii (Fig. 1.1).

Few organs carry such capacity to convey and evoke emotion. The experiments of Hooker and Humphrey, for example, provide unequivocal video evidence that localized tactile stimulation of the skin of the human embryo as early as 8–9 weeks’ gestation will evoke a reflex response.^{2,3} Thus, even early in development, the skin cannot be considered apart from the developing central nervous system and other fetal organs, nor, as will be demonstrated in this chapter, from the changing dynamics of its aqueous environment and maternal enclosure.

Fetal skin development occurs in a unique physiological world. The normal intrauterine environment is profoundly hypoxic, a condition aptly described by the eminent fetal physiologist, Joseph Barcroft, as ‘Mt Everest in utero.’⁴ Fetal wounds heal with little or no scarring.⁵ Touch, the first sense to develop in all vertebrates,⁶ occurs in a milieu where stimuli are muted and receptor pathways may be immature.⁷ The electrical impedance of the fetal skin is inconstant and increases markedly in mid-gestation.⁸ The fetus develops in an environment of relative immune privilege⁹ and critical protective functions of the skin, which are unnecessary prenatally, must be operative immediately at birth, e.g., protection from environmental trauma, infection, cold, and xeric stress.¹⁰

Comparison of human fetal skin development to other well-studied animal models highlights important and peculiar differences. Humans, for example, have a relatively long gestation (Table 1.1). Human infants have a prolonged postnatal period of vulnerability when maternal bonding and skin-to-skin contact figure prominently. According to Brazelton, the human neonate, in contrast to other species, is relatively precocious in sensory capabilities and relatively helpless in motor skills.¹¹ This developmental disparity places a premium on understanding the intrauterine maturation of the skin as a sensory organ and the impact of cutaneous function on the developing nervous system.¹² Dermatologists and skin scientists will note that humans are distinguished from other primates, not merely by opposable thumbs and a large, versatile brain but most obviously by a body surface, which is strikingly furless, vulnerable, and characterized by an expanse of well-developed interfollicular epidermis, earning humans the designation, the ‘Naked Ape.’¹³

In contrast to term gestation, the border of viability is the gestational age when the prematurely delivered fetus can survive in the extrauterine environment. In humans, this border, dependent in part upon medical intervention, exhibits racial and gender differences and varies from country to country, but is typically placed at 23–25 weeks’ gestation.¹⁴ This is parenthetically the time of formation of the epidermal barrier, i.e., that skin structure critical for postnatal transition and survival.^{15,16}

Although typically outside the purview of traditional dermatology, the infant at birth benefits from desirable surface characteristics, including skin suppleness, softness, and smoothness as well as pheromonal influences, which positively influence maternal bonding and caregiver support.^{1,17,18} This positive perception of infant skin emphasizes the skin–brain connection and cannot be dismissed from dermatological inquiries in the newborn period. The quintessential maternal–infant bonding experience in *mammals*, i.e., breast-feeding, involves intimate skin-to-skin contact between mother and infant and the production of milk by an ectodermal, skin-based glandular derivative.¹⁹

In addition to normal physiological development, pathophysiological events may arise in utero with subsequent need for medical intervention. Innate immune mechanisms to combat chorioamnionitis, for example, are important in the last trimester, to forestall systemic inflammatory responses in the fetus which carry long-term neurological sequelae.^{10,20,21} Birth trauma from intrauterine events such as amniotic bands or iatrogenic incidents may arise along with a panoply of gene defects, leading to congenital skin disorders. Later chapters detail specific dermatological conditions, which have their roots in utero. New tools of molecular investigation and the possibility of intrauterine therapies are exciting new fields of research. Finally, recognition of the body surface as a critical interface for receiving and delivering care transcends specific diseases and includes a plethora of important functions such as skin adhesion, monitoring, topical wound care, bathing, cleansing, emolliency, and microbiome support.^{1,22} All of these skin-based functions have their beginning in the transition of the fetus to the infant at birth.

Timing of embryonic and fetal development

Important morphologic events in intrauterine skin development are illustrated in Table 1.2. In Table 1.2, estimated gestational age (EGA) refers to the system used in basic embryology texts and by researchers to refer to the age of the fetus.²⁴ In this system, fertilization occurs on day 1. However, the dating system used by obstetricians and other clinicians as a convenient method for staging pregnancy defines day 1 as the first day of

TABLE 1.1 Gestation lengths

Species	Gestation in days (approx.)
Laboratory mouse	20.5
Domestic rat	21.5
Domestic rabbit	32
Dog	57–63
Domestic cat	63
Guinea pig	68
Sheep	147
Monkey (rhesus)	165
Man	265

(Adapted from Bradley RM, Mistretta CM. Fetal sensory receptors. *Physiological Reviews* 1975; 55(3):352–382.)

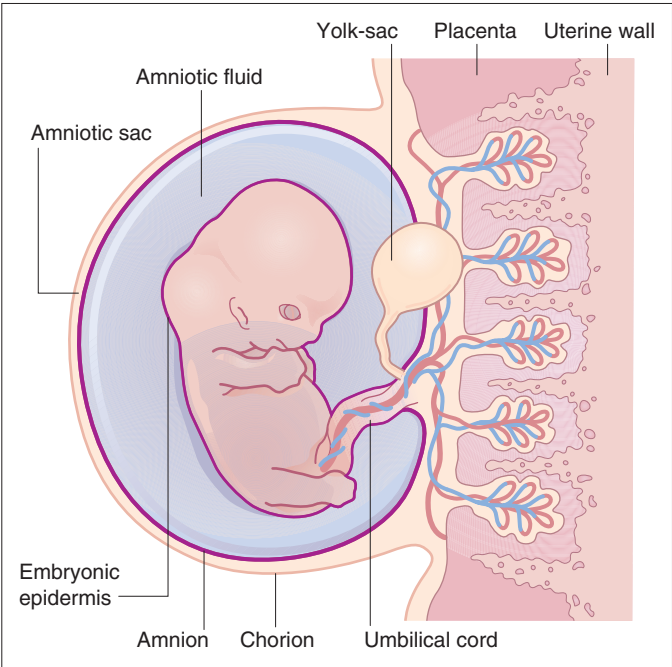


Figure 1.1 Embryo of approximately 8 weeks’ gestation (mid-first trimester) enclosed in amniotic fluid. The epidermis (embryonic ectoderm) is topologically continuous with the amnion (extraembryonic ectoderm) via the umbilical cord. The extraembryonic membranes (amnion and chorion) are shed at the time of birth along with the placenta and scission of the umbilical cord. The embryonic ectoderm also develops into the nervous system (not shown).

– *organogenesis*, *histogenesis*, and *maturation*²⁶ – that correspond roughly to the embryonic period (0–60-plus days); the early fetal period (60 days to 5 months); and the late fetal period (5–9 months) of development. The first stage, *organogenesis*, involves the specification of ectoderm lateral to the neural plate to become epidermis and the allocation of subsets of mesenchymal and neural crest cells to become dermis. During this stage, embryonic ectoderm and mesoderm become physically apposed, and they initiate the signaling cross-talk necessary for basement membrane and subsequent skin appendage (hair, nail, and sweat gland) formation.

The second stage, *histogenesis*, is characterized by dramatic morphologic changes in the presumptive skin, including epidermal stratification, epidermal appendage involution and differentiation, mesenchymal subdivision of the dermis and hypodermis, and vascular neogenesis. The third stage, *maturation*, entails the functional evolution of these skin components, so that they provide adequate thermoregulatory capacity, surface tensile strength, and barrier function for postnatal survival in the harsh, arid, nonsterile extrauterine environment. The remainder of this chapter highlights selected events of structural development of the skin in utero along with important physiological and clinical correlates.

Epidermis

EMBRYONIC DEVELOPMENT

During the third week after fertilization, the human embryo undergoes gastrulation, a complex process of involution and cell redistribution that generates the three primary embryonic germ layers: endoderm, mesoderm, and ectoderm.²⁴ Shortly after gastrulation, the ectoderm is further subdivided into neuroectoderm, a medial strip parallel to the long axis of the developing embryo, and presumptive epidermis on either side of this strip. Neurulation results in infolding of the embryonic ectoderm to become the neural tube and subsequent brain and spinal cord (Fig. 1.2). The extraembryonic ectoderm (lateral to the epidermis) becomes the amnion lining the amniotic sac. The early presumptive epidermis is a loosely associated single cell layer.²⁹ By 6 weeks’ EGA (8 weeks’ LMP), the surface ectoderm covering most regions of the body already consists of basal cells and more superficial periderm cells (Fig. 1.3).^{30,31} The periderm layer is a transient embryonic layer that does not participate in the production of definitive epidermal progenitors. The presumptive epidermis at these early stages is not considered a true stratified epithelium.

The basal cells of the embryonic epidermis display morphologic and biochemical features similar – but not identical – to basal cells of later developmental stages. Embryonic basal cells are slightly more columnar than later fetal basal cells and lack morphologically distinct hemidesmosomes.^{32,33} Matrix adhesion molecules critical for histogenesis and signal transduction, such as E- and P-cadherins and integrins β -1 and β -4, exhibit spatially and temporally coordinated expression in the developing epidermis.³⁴ The keratin pair K8/K18, typically found in simple epithelial cells, is the first pair expressed in embryogenesis³⁵ and may represent the oldest phylogenetic keratins.³⁶ Keratins involved in higher order tonofilament formation such as K5/K14 can also be identified.

Periderm cells of the embryonic epidermis are larger and flatter than the underlying basal cells. As such, periderm cells

TABLE 1.2 Landmarks in human fetal skin development relevant to prenatal diagnosis	
Structure or event	Estimated gestational age (weeks)
Epidermal stratification and expression of K5, K14 and K1, K10	6
Presence of melanocytes and Langerhans’ cells in the epidermis	8
Formation of complete hemidesmosomes, anchoring filaments, and anchoring fibrils	8–10
Formation of the nail primordium	10
Initiation of hair follicles	12
Initiation of eccrine sweat glands on the palms and soles	10–12
Delineation of papillary and reticular dermis	11–12
Formation of adipose tissue in hypodermis	15
Follicular keratinization	15
Interfollicular keratinization	22–24
Formation of eccrine sweat glands on the body	24–26

(Adapted from Holbrook KA, Smith LT, Elias S. Prenatal diagnosis of genetic skin disease using fetal skin biopsy samples. Archives of Dermatology 1993; 129(11):1437–1454.)

the last menstrual period (LMP) and is synonymous with menstrual age.²⁵ In this dating system, fertilization occurs on approximately day 14. Thus, a woman who is 14 weeks’ pregnant (LMP) is carrying a 12-week-old fetus (EGA).

From a functional point of view, fetal skin development can be divided into three temporally overlapping stages

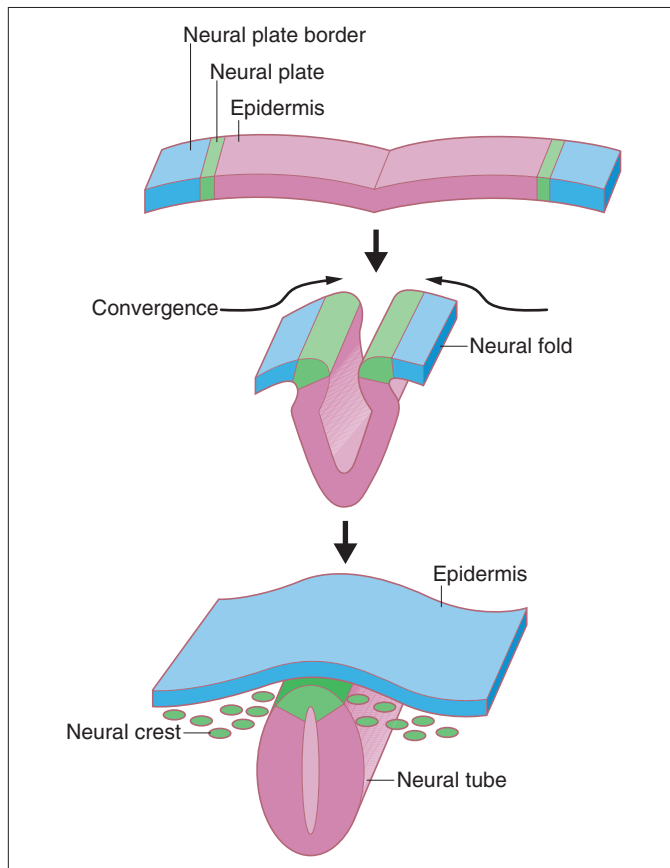


Figure 1.2 The process of neurulation and the formation of the neural crest. During the 3rd to 4th week of gestation, following gastrulation, formation of the neural tube segregates specific populations of ectodermal cells destined to form the brain and spinal cord (neural tube), epidermis (embryonic surface ectoderm), and amnion (extraembryonic ectoderm). The neural crest consists of a migratory cell population, which forms melanocytes, Schwann cells, adrenal medulla, facial cartilage, etc.²⁷ These complex embryological invaginations and evaginations convert the previous spheroid into a topologically more complex toroidal form.²⁸

have been termed a ‘pavement epithelium’.^{30,37} Apical surfaces in contact with the amniotic fluid are studded with microvilli. Their lateral surfaces in contact with adjacent peridermal cells are sealed with tight junctions, possibly precluding passive – but not active – diffusion of fluids across this outer layer of the embryo. Periderm cells, like the embryonic basal cells, express the stratified epithelial keratins K5 and K14, but also express simple epithelial keratins K8, K18, and K19.^{38,39} Towards the end of the second trimester these superficial cells are eventually sloughed.⁴⁰

EARLY FETAL DEVELOPMENT

By the end of 8 weeks’ gestation (10 weeks’ LMP), the basic components of most organ systems have been laid down and hematopoietic production has shifted to the bone marrow. This marks the classic division between embryonic and fetal development, and it corresponds to initial epidermal stratification and the formation of the third ‘intermediate’ layer between the two pre-existing cell layers (Fig. 1.3). Cells in the intermediate layer of the early fetal epidermis express the K1/10 skin differentiation-type keratin markers, as well as the desmosomal

protein desmoglein 3, which is also known as the pemphigus vulgaris antigen.^{41,42} Moreover, intermediate filaments and desmosomal junctions are more abundant in this layer than in the basal or periderm layers. In contrast to the spinous cells of the mature nonwounded epidermis, cells within the intermediate layer remain highly proliferative.^{43,44} Over the next several weeks, more layers are gradually added to this intermediate zone of the developing epidermis, such that by 22–24 weeks’ EGA, the epidermis contains four to five layers in addition to terminal differentiation of the periderm with formation of a cross-linked cornified envelope (Fig. 1.4).⁴⁵

After the onset of stratification, the basal layer also displays characteristic morphologic and biochemical changes. Basal cells become more cuboidal and begin to synthesize other keratin peptides, including K6, K8, K19, and the K6/K16 hyperproliferative pair.^{38,39} This latter keratin pair is not normally expressed in mature interfollicular epidermis but is upregulated in response to wounding and hyperproliferative conditions.⁴⁶ During early fetal development, the basal cell layer also begins to express the hemidesmosomal proteins BPA1 and BPA2, and to secrete collagen types V and VII, the latter being the major component of the anchoring fibrils of the dermis.^{41,47–49} DNA-labeling studies indicate that by 80–90 days’ EGA, a distinct subset of slow-cycling cells exists within the basal cell population, suggesting that an epidermal stem cell population has already been set aside at these early stages.⁴⁴

LATE FETAL DEVELOPMENT

Maturation of the epidermis during late fetal development is characterized by the generation of granular and stratum corneum (SC) layers, the formation of a water-impermeable barrier, and the sloughing of the periderm. Keratinization, the terminal differentiation seen in the stratum granulosum (SG) and SC, is initiated first in the skin appendages between 11 and 15 weeks’ EGA, and extends to the interfollicular epidermis from about 22–24 weeks’ EGA.^{38,39} During the third trimester, the cornified cell layers increase in number, aiding in the formation of a barrier.

The prenatal epidermal water permeability barrier was previously thought to be derived almost entirely from lipid secreted from cells of the outer SG and processed to highly hydrophobic species in the SC interstices, controlled not only by the intrinsic program of epidermal barrier development but also by prenatal exposure to fetal or maternal hormones,⁵⁰ nutrient gradients,⁵¹ or by air exposure at birth. In postnatal humans and rodents, this epidermal permeability barrier is formed by polar lipids secreted from the SG that are then processed into impermeant lamellar bilayers.^{52–56} In contrast, since prior freeze-fracture electron microscopy studies showed only discontinuous tight junction (TJ) strands in adult mouse epidermis,⁵⁷ it was widely thought that in contrast to amphibian skin or other ‘tight’ mammalian epithelium (such as kidney), TJ played only a minor role in the epidermal water permeability barrier.

Although congenital human skin diseases caused by mutations in TJ are rare,⁵⁸ common diseases such as atopic dermatitis have been linked with acquired TJ dysfunction.⁵⁹ Further, studies show that claudin-1 deficient mice suffer barrier defects leading to death soon after birth.⁶⁰ Involucrin-Cldn6 (Inv-Cldn6) transgenic mice also display skin barrier defects, the severity of which is dependent upon the level of Cldn6 over-expression.⁶¹ These results suggest that TJ also plays an important role in forming

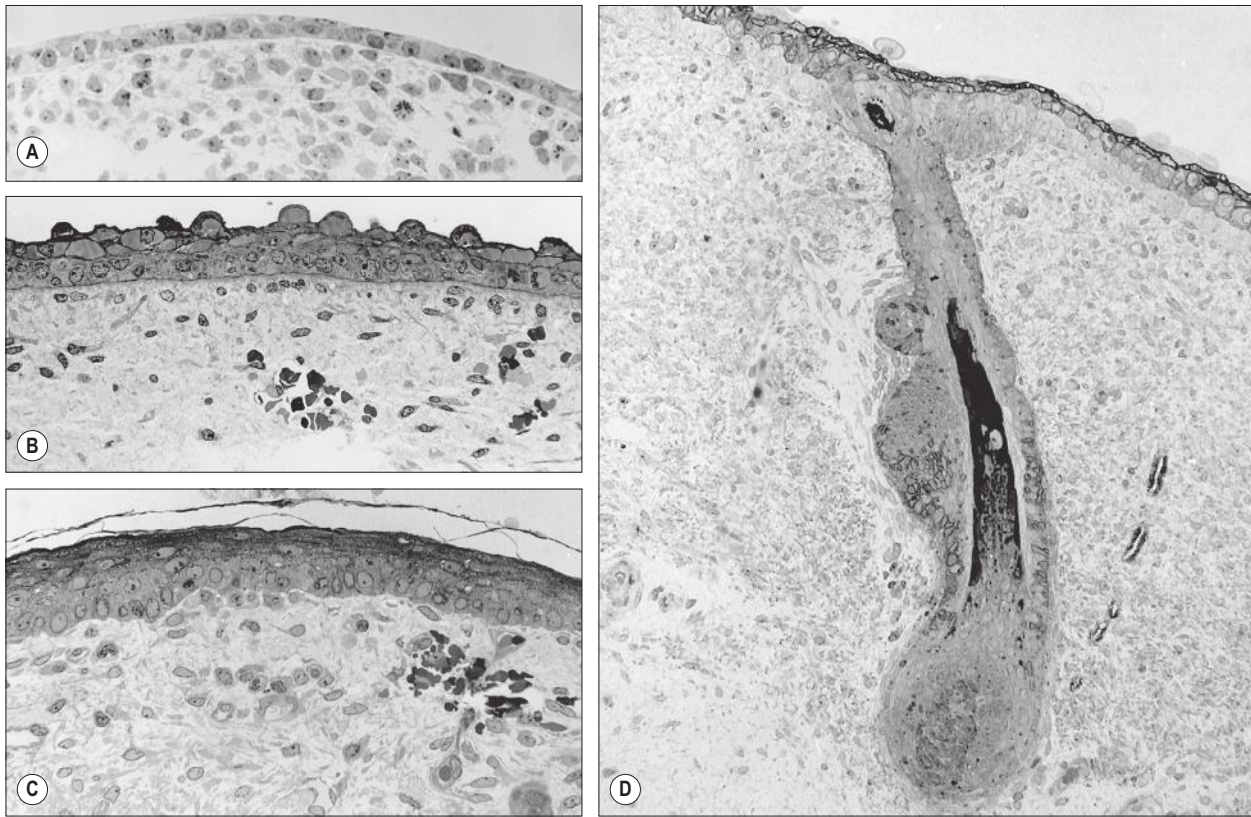


Figure 1.3 Epidermal morphogenesis. (A) At 36 days the epidermis consists only of a basal layer and a superficial periderm layer. (B) By 72 days a well-formed intermediate layer is present between the basal and periderm layers. By the end of the second trimester, there are several intermediate cell layers and the stratified epidermis begins to keratinize. (C) In neonatal skin, a distinct granular layer and stratum corneum are present. Hair follicles first begin to bud down in the dermis between 75 and 80 days. (D) An early bulbous hair peg-stage follicle from a mid-second trimester fetus. (Photomicrographs courtesy Dr Karen Holbrook.)

the epidermal permeability barrier during the prenatal period, or in regulating the subsequent development of the lipid barrier.

CLINICAL RELEVANCE

Gross defects in early epidermal specification and organogenesis are rarely observed in the neonate, probably because they are incompatible with fetal survival. Using mice as an animal model system, researchers demonstrated that obliteration of the p63 gene precludes the formation of most multilayered epithelia in the body, leading to perinatal lethality due to loss of skin barrier function. Humans who carry mutations in this gene still retain some functionality and therefore display less severe alterations in their epidermis and appendages (see below).

In contrast, congenital defects in epidermal maturation are not uncommon, as they do not usually impinge on in utero survival. Lamellar ichthyosis (see [Chapter 19](#)) is usually inherited in an autosomal recessive manner and in 30% of patients is caused by mutations in the gene encoding epidermal transglutaminase,^{62–64} the enzyme that cross-links submembranous proteins to form the insoluble cornified envelope of the SC. In its absence, large, dark polygonal scales form over the entire body, and at birth, the infant may be transiently wrapped in a waxy, collodion-like membrane.⁶⁵ A similar clinical presentation can be seen in patients homozygous for mutations in the

ABCA12 gene, which encodes an ATP-binding cassette thought to be important for lipid trafficking across keratinocyte membranes. Infants with the more severe ‘harlequin ichthyosis’ (see [Chapter 19](#)) are born encased in armor-like, thickened, adherent SC which cracks upon exposure to air.^{66–68} This extreme variant also appears to be due to mutations in the *ABCA12* gene.

In contrast to the permanent manifestations of genetic defects, the inadequate epidermal keratinization and maturation of the premature epidermis are transient. Immaturity of the SC, especially in infants born before 28 weeks’ EGA (30 weeks’ LMP), places these neonates at increased risk for dehydration, excessive penetration of topical drugs or other chemicals, and infection from organisms newly colonizing the skin (see [Chapters 4 and 5](#)).^{69–74} In general, even full-term newborns display a somewhat reduced barrier function, and continued maturation occurs over the first few weeks of life, such that by 3 weeks of age, the newborn’s SC is structurally and functionally equivalent to that of the adult; maturation is accelerated in the premature infant, although the duration may be longer in extremely premature infants.^{69,75}

SPECIALIZED CELLS WITHIN THE EPIDERMIS

Two major immigrant cells – melanocytes and Langerhans’ cells – populate the epidermis during early embryonic development. Melanocytes are derived from a subset of neuroectoderm cells,

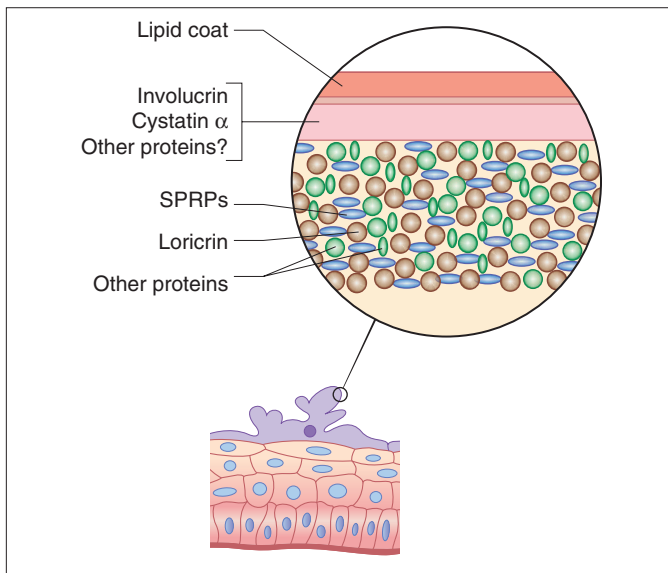


Figure 1.4 Formation of the cornified cell envelope (CCE) in human periderm.⁴⁵ Following epidermal stratification between 96–160 days EGA, the outermost periderm undergoes terminal differentiation with formation of the CCE. Covalent cross-linking mediated by transglutaminase results in a high molecular weight polymeric structure composed of loricrin, small proline-rich proteins (SPRPs), involucrin, cystatin α , and other proteins. The outermost lipid coating is also covalently cross-linked yielding an insoluble periderm cell which is sloughed to the amniotic fluid. A similar process of CCE formation occurs later in gestation in the formation of vernix caseosa and the interfollicular stratum corneum. (Adapted from Akiyama M, Smith LT, Yoneda K, Holbrook KA, Hohl D, Shimizu H. Periderm cells form cornified cell envelope in their regression process during human epidermal development. *Journal of Investigative Dermatology* 1999; 112(6):903–909.)

the neural crest, which forms along the dorsal neural tube and gives rise to a variety of cell types, including many tissues of the face and peripheral autonomic neurons.²⁷ Neural crest cells destined to become melanocytes migrate away from the neural tube within the mesenchyme subjacent to the presumptive epidermis. They migrate as semicoherent clones laterally and then ventrally around the trunk to the thoraco-abdominal midline, anteriorly over the scalp and face, and distally along the extremities. Postnatally, the embryonic paths taken by these partially coherent clones can be readily visualized in patients with banded pigmentary dyscrasias following Blaschko's lines, such as the disorders classified as hypomelanosis of Ito, and linear and whorled hypermelanosis (see [Chapters 23 and 24](#)).^{76,77}

Melanocytes are first detected within the epidermis of the human embryo at approximately 50 days' EGA, recognized by their dendritic morphology and their specific immunoreactivity.⁷⁸ Even at these early developmental timepoints, the density of melanocytes is quite high (1000 cells/mm²).⁷⁹ The density increases further around the time of epidermal stratification (80–90 days' EGA) and initiation of appendageal development. Between 3 and 4 months EGA, depending on body site and the race of the fetus, melanin (visible pigment) production becomes detectable, and by 5 months, melanocytes begin transferring melanosomes to the keratinocytes, a process that will continue after birth.^{80–82} Although all melanocytes are in place at birth and melanogenesis is well under way, the skin of the newborn infant is not fully pigmented and will continue to darken over the first several months. This is most apparent in individuals with darker skin.

Langerhans' cells, the other major immigrant population, are detectable within the epidermis by 40 days' EGA.⁸³ Similar to melanocytes, the early embryonic Langerhans' cells do not yet possess the specialized organelles characteristic of mature cells, but can be distinguished from other epidermal cells by their dendritic morphology, immunopositive reaction for the HLA-DR surface antigen, and high levels of ATPase activity. After the transition from embryo to fetus, they begin to express the CD1 antigen on their surface and to produce characteristic granules of mature Langerhans' cells.^{83,84} Although the extent of dendritic processes from individual Langerhans' cells increases during the second trimester, the total number of cells remains low and only increases to typical adult numbers in the third trimester.⁸⁵

Another distinct subset of cells within the basal cell layer are Merkel cells, which are highly innervated neuroendocrine cells involved in mechanoreception. Merkel cells can be round or dendritic, and are found at particularly high densities in volar skin. They are frequently associated with epidermal appendageal structures and are occasionally detected within the dermis. Their distinguishing morphologic and immunohistochemical features are cytoplasmic dense-core granules, keratin 18, and neuropeptide expression, which can be detected as early as 8–12 weeks' EGA in palmoplantar epidermis and at slightly later times in interfollicular skin.⁸⁶ Recent keratin expression data, as well as transplant studies, suggest that Merkel cells are derived from pluripotent keratinocytes, rather than neural progenitors such as neural crest, but the results are not conclusive.^{86–88}

CLINICAL RELEVANCE

Many clinical defects are known to affect normal pigmentation. Defects in melanoblast migration, proliferation, and/or survival occur in several clinical syndromes, and many of the genetic mutations responsible for these defects have been identified (see [Chapter 23](#)). Failure of an adequate number of melanoblasts to completely supply distal points on their embryonic migration path occurs in the different types of Waardenburg syndrome, as well as in piebaldism, resulting in depigmented patches on the central forehead, central abdomen, and extremities. These defects are associated with mutations in several different genes, including genes encoding transcription factors, such as Pax3 and MITF, as well as membrane receptors and their ligands, such as endothelin 3, endothelin-receptor B, and *c-kit*.^{89–91} In albinism, however, melanocyte development is normal, but production of pigment or melanin is inadequate. The most severe form of oculocutaneous albinism results from null mutations in the gene encoding tyrosinase, the rate-limiting enzyme in the production of melanin. Less severe forms of albinism are caused by mutations in tyrosinase alleles, which lead to partial loss of function, as well as by mutations in other genes encoding proteins important in melanin assembly in melanosomes or transport.⁹²

NERVES AND VASCULATURE

Development of the cutaneous innervation closely parallels that of the vascular system in terms of its pattern, rate of maturation, and organization. Nerves of the skin consist of somatic sensory and sympathetic autonomic fibers, which are predominantly small and unmyelinated. Localized somatosensory reflexes can first be elicited using von Frey hairs in the perioral area of the

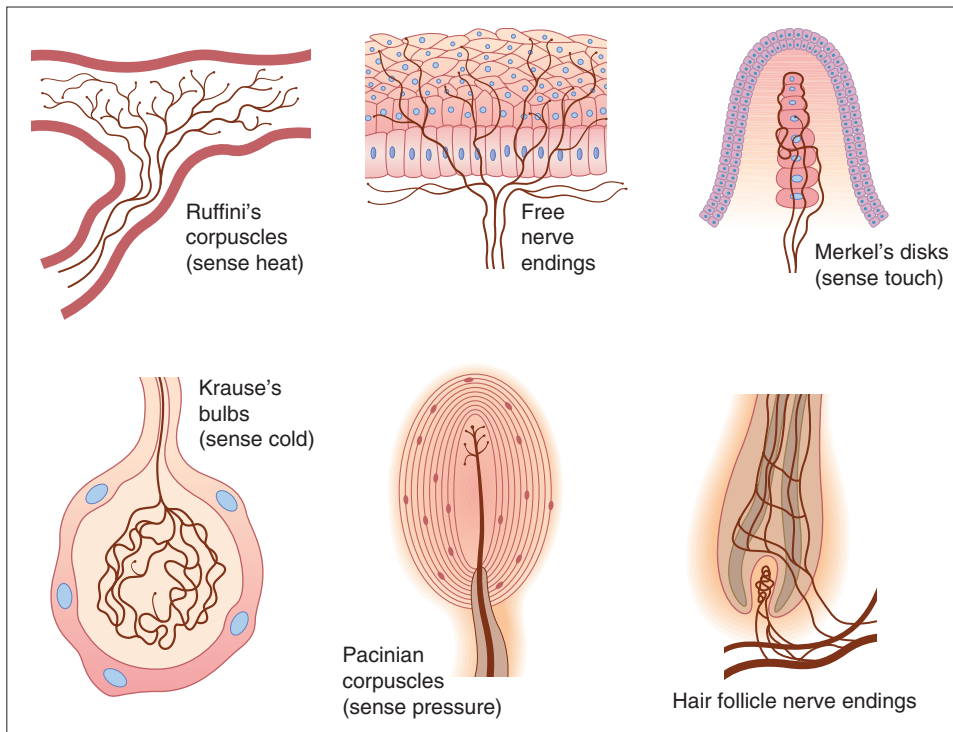


Figure 1.5 Variety of cutaneous nerve endings in the human fetus.⁹⁶ Free nerve endings are present in oro-facial skin as early as 8–9 weeks' gestation.⁷ Specialized nerve endings such as Pacinian corpuscles, Merkel's disks, etc., which are known to modulate different cutaneous stimuli in adults are also present in the fetus.^{7,93,96–98} Other than touch and reflex withdrawal, however, the functional correlates of fetal cutaneous receptors are obscure and difficult to investigate.

7.5-week fetus, at which time free nerve endings can be visualized beneath the epithelium.^{7,93,94} The growing sensory nerve endings, therefore, are presumably sensitive to mechanical stimuli transmitted through the fetal skin. Cauna and Mannan have suggested that the developing nerve plexus as a whole functions as a receptor in early development to be superseded by more definitive end organs later in gestation.⁹⁵

Various specialized nerve endings have been well-documented in embryonic and fetal skin (Fig. 1.5).⁷ Work by Paus, Slominski, and others has highlighted novel neuroimmunoendocrine functions of postnatal skin.^{99,100} The stress hormone cortisol, for example, can be manufactured *de novo* by the human hair follicle¹⁰¹ and is present on preterm SC.¹⁰² These exciting new developments place a premium on better understanding the skin–brain connection during normal development, as well as in conditions such as the neurocristopathies, neurofibromatosis, incontinentia pigmenti, tuberous sclerosis and other diseases highlighted in later chapters. The importance of early fetal *somatic* (i.e., muscle) innervation to normal skin morphogenesis is the recent demonstration that lack of the fetus-specific component of the acetylcholine receptor produces the extensive dermal webbing seen in multiple pterygium syndrome.¹⁰³

The development of the cutaneous vascular system is dynamic and dependent on gestational age, body site, and function, among other factors. Vessels of the endoderm–mesoderm interface form through the in-situ differentiation of endothelial cells (vasculogenesis).^{104,105} Originally, they form horizontal plexuses within the subpapillary and deep reticular dermis, which are interconnected by groups of vertical vessels. This vascular framework has been elegantly reconstructed by the use of computer graphics to illustrate the complexity that already exists by 45–50 days' EGA.¹⁰⁶ Such structure does not remain constant even throughout fetal life, but varies depending on the body region and gestational age, as well as on the presence of hair follicles and glands that may require an increased blood

supply. Furthermore, vascular emergence and development correlate directly with the particular tissue, determined specifically by the influences of pressure and function.

Regional variation also depends on gestational age. Blood vessels have been identified in fetal skin as early as 9 weeks' EGA. At this stage, they help delineate the dermal–hypodermal junction. By 3 months, the distinct horizontal and vertical networks have formed. And by 5 months, vasculogenesis has largely ceased and the formation of the complex vascular plexus is initiated by angiogenesis, the budding and migration of endothelium from pre-existing vessels. With increasing gestational age, the superficial architecture becomes more organized, culminating at birth in an extensive capillary network responsible for the skin redness often observed in the newborn. Within the first few postnatal months the complexity decreases as skin surface area increases, lanugo hairs are lost, and sebaceous gland activity decreases. It is during this time that the rate of skin growth is greatest. By approximately 3 months of age, the vascular patterns more closely resemble those of the adult.

Not only do the number and caliber of the blood vessels change over time, so too does the direction of blood flow. Considering the dynamic nature of this circulatory system, it is not surprising that, of the malformations and tumors seen in newborns, vascular anomalies are the most common.

Errors in neurovascular morphogenesis likely lead to several relatively common syndromes such as Klippel–Trenaunay, Sturge–Weber and PHACE syndromes. See [Chapters 21](#) and [22](#) for further discussion of these topics.

Dermis and subcutis

OVERVIEW

The fully developed dermis is characterized by complex interwoven collagen and elastic fibers enmeshed in a proteoglycan

matrix. Fibroblasts, mast cells, and macrophages are scattered throughout the dermis, and nerve fibers and vascular networks course through it, dividing it into distinct domains. In contrast, the embryonic dermis is quite cellular and amorphous, lacking organized extracellular fibers. Embryonic mesenchymal cells capable of differentiating into a wide variety of cell types are embedded in a highly hydrated gel, rich in hyaluronic acid. Moreover, only a few nerve fibers have reached this peripheral location, and vessels have not evolved into their mature patterns. During the course of fetal development, this so-called cellular dermis, which is conducive to cell migration and tissue remodeling, is transformed into the fibrillar dermis of the adult, which provides increased strength, resilience, and structural support.¹⁰⁷

EMBRYONIC DERMAL DEVELOPMENT

The specification and allocation of dermal mesenchymal cells are rather complex and not well understood. The cell of origin for the presumptive dermis depends on its anatomic location. The dermis of the face is derived from neural crest cells; that of the dorsal trunk is derived from the dermatomyotome portion of the differentiated somite; and the dermis of the limbs is derived from the lateral plate (somatic) mesoderm.^{107,108} Regional patterning of the skin and differences in the type and quality of the epidermal appendages produced in the older fetus might in part reflect these early differences in dermal cell precursors. In addition, signaling from adjacent tissues plays a critical role.^{109,110}

By 6–8 weeks' EGA, the presumptive dermal cells already underlie the epidermis. However, there is, as yet, no sharp demarcation between cells giving rise to skin dermis and those giving rise to musculoskeletal elements. Electron microscopic (EM) studies of the presumptive dermis at these stages demonstrate fine filaments, but rarely fibers.¹¹¹ Although most protein components of collagen fibers and some microfibrillar components of elastin fibers (fibrillin) are synthesized by the embryonic dermal cells, the proteins are not yet assembled into large, rigid fibers.^{49,112} Moreover, the ratio of collagen III to collagen I is 3:1, the reverse of that in the adult.^{49,113,114}

FETAL DERMAL DEVELOPMENT

After embryonic–fetal transition at 60 days, the presumptive dermis is distinguishable from the underlying skeletal condensations. Moreover, within the dermis, there is a progressive change in matrix organization and cell morphology, such that by 12–15 weeks, the fine interwoven mesh of the papillary dermis adjacent to the epidermis can be distinguished from the deeper, more fibrillar reticular dermis.^{49,112} Large collagen fibers accumulate in the reticular dermis during the second and third trimesters. Definitive elastin fibers first become detectable by EM studies around 22–24 weeks' EGA,¹¹⁵ although both the microfibrillar protein fibrillin and the microfibrillar structures, which are morphologically similar to elastin-associated microfibrils of the adult, can be detected at earlier stages.¹¹² By the end of gestation, the dermis is thick and well organized, but is still much thinner than in the adult and has a higher water content, reminiscent of the fetal dermis. Dermal maturation is marked by increasing tensile strength and the transition from a nonscarring to a scarring response after wounding. Thus, fetal skin biopsies tend to heal with little evidence of the surgical

event. This has obvious clinical implications, and the molecular controls critical for nonscarring fetal wound healing are an area of active research (Table 1.3).^{5,116,117}

CLINICAL RELEVANCE

Congenital defects in the specification and development of the dermis are probably incompatible with survival to term, although there are a few exceptions. Infants with restrictive dermopathy disorder, which is characterized by a thin, flat dermis, lack of elastic tissue fibers, and shortened appendageal structures, do survive to birth but then die in the neonatal period, partly because of insufficient elaboration of the dermis.^{118,119} This disorder is caused by mutations in either the *LaminaA* gene or the gene encoding the *LaminaA* processing enzyme. Another syndrome characterized by inadequate dermal development is Goltz syndrome (focal dermal hypoplasia).^{65,120} This is an X-linked dominant condition caused by mutations in the *PORCN* gene, in which most males who inherit the mutation on their single X chromosome die in utero. In contrast, females are functional mosaics as a result of random X-inactivation early in embryogenesis, and those with Goltz syndrome display areas of dermal hypoplasia where the mutant X is active. These bands of dermal hypoplasia follow Blaschko's lines and alternate with bands of normal dermal development where the normal X is active.^{121,122}

DEVELOPMENT OF THE HYPODERMIS AND ADIPOSE TISSUE

The hypodermis can be delineated by 50–60 days' EGA.²⁶ It is a distinct region that is separated from the overlying cellular dermis by a plane of thin-walled vessels. Toward the end of the first trimester, the sparse matrix of the hypodermis can be distinguished morphologically from the slightly denser, more fibrous matrix of the dermis.^{107,123} In the second trimester, mesenchymally derived preadipocytes begin to differentiate and accumulate lipids¹²⁴ and by the third trimester, the more mature adipocytes are aggregated into large lobules of fat divided by fibrous septa. In addition to a passive fat reserve for the body, recent evidence supports an active endocrine role for adipose tissue with effects on vascular and immune function.¹²⁵ An example is the gene that encodes leptin, whose abnormal regulation has been implicated in the pathogenesis of obesity.

Combined dermoepidermal structures

DERMOEPIDERMAL JUNCTION

The dermoepidermal junction (DEJ) is the region where the epidermis and dermis abut. In the broadest definition, it includes the specialized extracellular matrix on which the basal keratinocytes sit, known as the basement membrane, as well as the basal-most portion of the basal cells and the superficial-most portion of the dermis. Importantly, both dermal and epidermal compartments contribute to the molecular synthesis, assembly, and integration of this region.

A simple basement membrane, separating the dermis and epidermis, can be discerned as early as 8 weeks' EGA. The basic protein constituents common to all basement membranes can

TABLE 1.3 Comparison of fetal wound healing profile with postnatal wound healing

Growth factors	Fetal regenerative phenotype	Postnatal scar formation
bFGF	Lower	Higher
PDGF	Lower	Higher
VEGF	Higher	Lower
TGF- β		
TGF- β 1	Low levels	High levels
TGF- β 2	Low levels	High levels
TGF- β 3	High levels	Low levels
Inflammatory response		
Inflammatory cell	Minimal	High levels leukocytes, macrophages, mast cells infiltrate
Cytokines		
Proinflammatory: IL-6, IL-8	Low levels	High levels
Anti-inflammatory: IL-10	High levels	Low levels
Extracellular matrix		
Collagen		
Histology	Fine, reticular weave	Thick, rope-like bundles
Type III collagen	High levels	Low levels
Deposition	Immediate	Delayed
Cross-linking	Low levels	High levels
TGF- β 1-stimulated deposition	Absent	Present
Hyaluronan		
Expression	High levels – Persistent expression	Low levels – Transient expression
Molecular weight	High	Low
HA receptors (fibroblast)	High levels	Low levels
Mechanical force		
Myofibroblast (day 14)	Absent	Present
Stem cells		
MSC	High levels	Lower levels
Dot cells	Present	Absent

bFGF, basic fibroblast growth factor; HA, hyaluronan; MSC, mesenchymal stem cell; PDGF, platelet-derived growth factor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor.

(Adapted from Leung A, Crombleholme TM, Keswani SG. Fetal wound healing: implications for minimal scar formation. *Current Opinion in Pediatrics* 2012; 24(3):371–378.)

already be detected immunohistochemically at this stage.^{32,47,126} These include collagen IV, laminin, and heparin sulfate and proteoglycans.

Specialized components of the DEJ do not appear until after the embryonic–fetal transition, around the time of initial epidermal stratification.^{32,47,126} With a few exceptions, all basement membrane antigens are in place by the end of the first trimester.²⁶ As discussed, the α 6 and β 4 integrin subunits are expressed quite early by embryonic basal cells.³² However, they do not become localized to the basal surface until after 9.5 weeks, which is coincident with the time when bullous pemphigoid antigens are first detected immunohistochemically and hemidesmosomes are recognized ultrastructurally.^{32,33,47,127} Similarly, anchoring filaments and anchoring fibrils, the basement membrane components that mediate basal cell attachment to extracellular matrix, are recognizable by 9 weeks' EGA.^{26,33} Collagen VII, the anchoring fibril protein, is detected slightly earlier, at 8 weeks.³³ Recent experimental data have delineated many of the molecular interactions crucial for connecting the cytoskeletal networks of the basal cells with the extracellular filamentous networks important in matrix adhesion (Fig. 1.6) (see Chapters 10 and 11).

CLINICAL APPLICATIONS

Several congenital skin blistering diseases result from mutations in genes encoding DEJ components (see Chapters 10 and 11).¹²⁸ The severity of the disorder, the exact plane of tissue separation, and the involvement of nonskin tissues depend in part upon which proteins are mutated. Because these blistering disorders are associated with a high postnatal morbidity and mortality they are frequent candidates for prenatal testing, identifying the responsible genetic mutation by chorionic villus sampling (CVS) or amniocentesis.

DEVELOPMENT OF APPENDAGES

Skin appendages (hair, nails, sweat and mammary glands in mammals, and feathers and scales in birds and reptiles) all consist of two distinct components: an epidermal component that elaborates the differentiated end-product, such as the hair or nail, and the dermal component that regulates specification and differentiation of the appendage. Fetal development of these structures depends on rigidly choreographed, collaborative interactions between early epidermis and dermis.^{107,129,130}

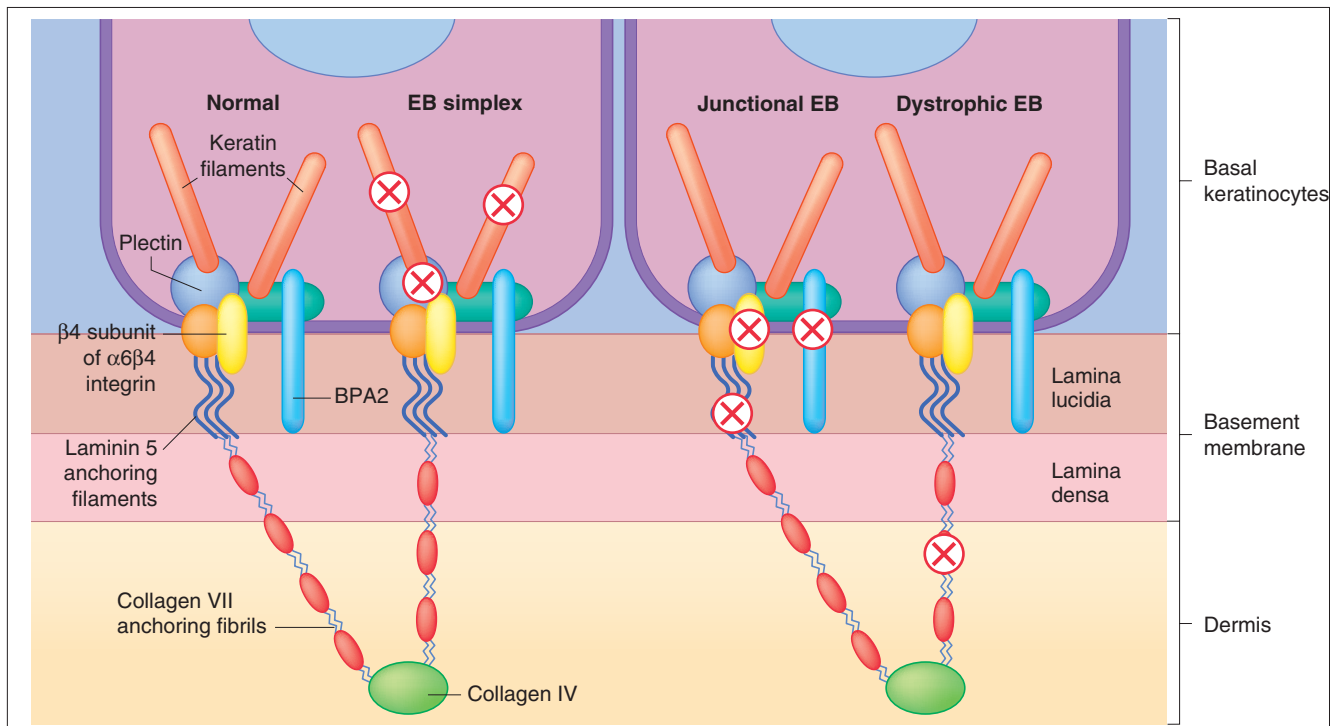


Figure 1.6 Schematic of the dermoepidermal junction indicating the proteins that are defective in the relevant hereditary bullous diseases (X). Mutations in genes encoding keratin 5 or keratin 14 cause epidermolysis bullosa (EB simplex). Plectin function is disrupted in EB associated with muscular dystrophy. One of the subunits of laminin 5 is defective in most forms of junctional EB. However, the $\beta 4$ subunit of $\alpha 6\beta 4$ integrin is altered in the form associated with pyloric atresia, and bullous pemphigoid antigen 2 (BPA2) is mutated in generalized atrophic benign EB. Collagen VII is defective in all forms of dystrophic EB published to date.

Defects in dermal induction or specification of the overlying ectoderm, or in the ectoderm's responses to these instructions, result in aberrant development, as has been demonstrated in genetic studies and transplant experiments in animal model systems.^{107,129–131} Moreover, the demonstration that defects in human homologs of mouse hairless, LMX1B, and tabby genes result in clinically significant developmental abnormalities in humans confirms the relevance of such animal studies to our understanding of human skin appendage development.^{132–136}

HAIR FOLLICLE AND SEBACEOUS GLAND DEVELOPMENT

Hair follicle formation begins on the head and then spreads caudally and ventrally in waves, resulting in regularly spaced rows and whorls of follicles.^{137,138} The first morphologic evidence of follicle formation in humans, the ectodermal placode, is the focal crowding of small groups of basal keratinocytes at regularly spaced intervals, starting between 75 and 80 days on the face and scalp.^{137–140} Slightly later in development, mesenchymal cell clusters are observed beneath these ectodermal placodes. Although morphologically similar to other dermal fibroblasts, these clustered mesenchymal cells are biochemically distinguishable based on their continued expression of certain molecular markers, such as nerve growth factor receptor (NGFR).²⁶ On the trunk at approximately 80 days' EGA, a cluster of basal epidermal cells thickens and begins to bud downward into the dermis, forming the early hair germs.^{140,141} Transplant studies in other species indicate that ectodermal budding requires an induction signal from the underlying mesenchymal cells. The cells of the early ectodermal bud or placode then respond with their own signal, which elicits a second mesenchymal signal. This second signal directs the species-specific type of mesenchymal appendage that will ultimately develop.^{107,129}

The next stage of hair development involves further proliferation and resulting downward elongation of the ectodermal bud, forming the so-called hair peg.¹³⁸ At 12–14 weeks' EGA, the hair peg develops a widened bulb at its base that flattens and then invaginates, engulfing the subjacent clustered mesenchymal cells, which become the follicular dermal papilla. In addition to the widened bulb at the base, two other bulges form along the length of the developing follicle, which is now termed the bulbous hair peg (see Fig. 1.3).^{138,142} The uppermost bulge is the presumptive sebaceous gland, and the middle bulge, which forms at approximately one-third the distance from the follicular base, is the site of the future insertion of the arrector pili muscle and is one location of multipotent stem cells, which give rise to all the progenitors necessary for regeneration of the lower portion of the follicle during postnatal follicular cycling, as well as to cells capable of replenishing the overlying epidermal covering in the event of extensive surface wounds or burns.¹⁴³

Maturation of the hair peg into a definitive follicle is a complex process involving the formation of a patent hair canal and the elaboration of at least six distinct concentric rings of cells.¹⁴⁴ The most peripheral ring of ectodermal cells makes up the outer root sheath, whose upper portion is continuous with the interfollicular epidermis and undergoes a similar process of keratinization. The lower portion of the outer root sheath, in contrast, does not form a granular layer or classic SC. The inner root sheath forms just internal to the outer root sheath. The cells in this sheath do form a granular layer through the keratin

proteins, and keratin-aggregating products produced here differ from those produced by the normal epidermis. Cells in this inner root sheath arise from self-renewing progenitor cells at the base of the follicle, which differentiate as they move upward toward the skin surface surrounding the hair shaft. Likewise, the three internal concentric layers of the hair shaft – cuticle, cortex, and medulla (from outer to inner) – arise from the matrix cells at the base of the follicle. These deep matrix cells sit on the basement membrane 'mat,' along the concavity of the hair follicle invagination in close proximity to the dermal papillae mesenchymal cells.

By 19–21 weeks' EGA, the hair canal has fully formed and the scalp hairs are visible just above the surface of the fetal epidermis.^{137,145,146} They continue to lengthen until 24–28 weeks, when they shift from the active growing phase (anagen) to the short-lived degenerative phase (catagen) and then to the resting phase (telogen).^{26,147} They then re-enter the active growing stage (second anagen), and the first wave of hairs is shed into the amniotic fluid as the new hairs grow out. Cycling through active and inactive phases continues for all hairs throughout the life of an individual,¹⁴⁸ although cycles for individual hairs become asynchronous postnatally. The maintenance of a tight anatomic relationship between dermal papilla cells and the cycling ectodermal portion of the hair follicle is critical for follicular self-renewal, and the inability to maintain this relationship results in a form of inherited alopecia, in which hair neogenesis is normal but, after the first resting phase, cycling is aberrant.¹³²

Perinatally the second wave of fine lanugo hairs is shed. With subsequent cycles, hairs increase in diameter and coarseness, forming first vellus and then adult-type terminal hair shafts on the scalp and brow.¹⁴⁷ During adolescence, vellus hairs of androgen-sensitive areas undergo a similar transition to terminal-type hair follicles.

Sebaceous gland maturation occurs in parallel with that of the follicle proper and begins between 13 and 16 weeks' EGA.¹⁴⁹ Lipogenic cells produced by the outer proliferative layer of the sebaceous gland progressively accumulate lipid/sebum until they terminally differentiate, which results in their disintegration and the release of their products into the upper portion of the newly formed hair canal.^{150,151} The synthesis and secretion of sebum is accelerated in the second and third trimesters under the influence of maternal steroids and/or fetal adrenal dihydroepiandrosterone.^{152–154} Of note, the first evidence of the human epidermal permeability barrier in utero is in the vicinity of the pilosebaceous unit.¹⁵ Sebaceous lipids are also a prominent component of vernix caseosa.¹⁵⁵ Fetal corneocytes associated with vernix may also derive from the pilosebaceous unit. Sebaceous gland hyperplasia and activity generally becomes quiescent during the first few postnatal months of life but may persist in cases of infantile acne (see Chapter 7).

NAIL DEVELOPMENT

The first evidence of nail formation is delineation of the flat surface of the future nail bed on the dorsal digit tip at 8–10 weeks,^{112,156} slightly earlier than the initiation of hair follicle development (Fig. 1.7). Along the proximal boundary of the early nail field a wedge of ectoderm buds inward at an oblique angle to the surface, forming the proximal nail fold. The presumptive nail matrix cells, which will give rise to the differentiated nail plate, reside on the ventral (deeper) side of the proximal invagination. At around 11 weeks, the dorsal surface of the nail

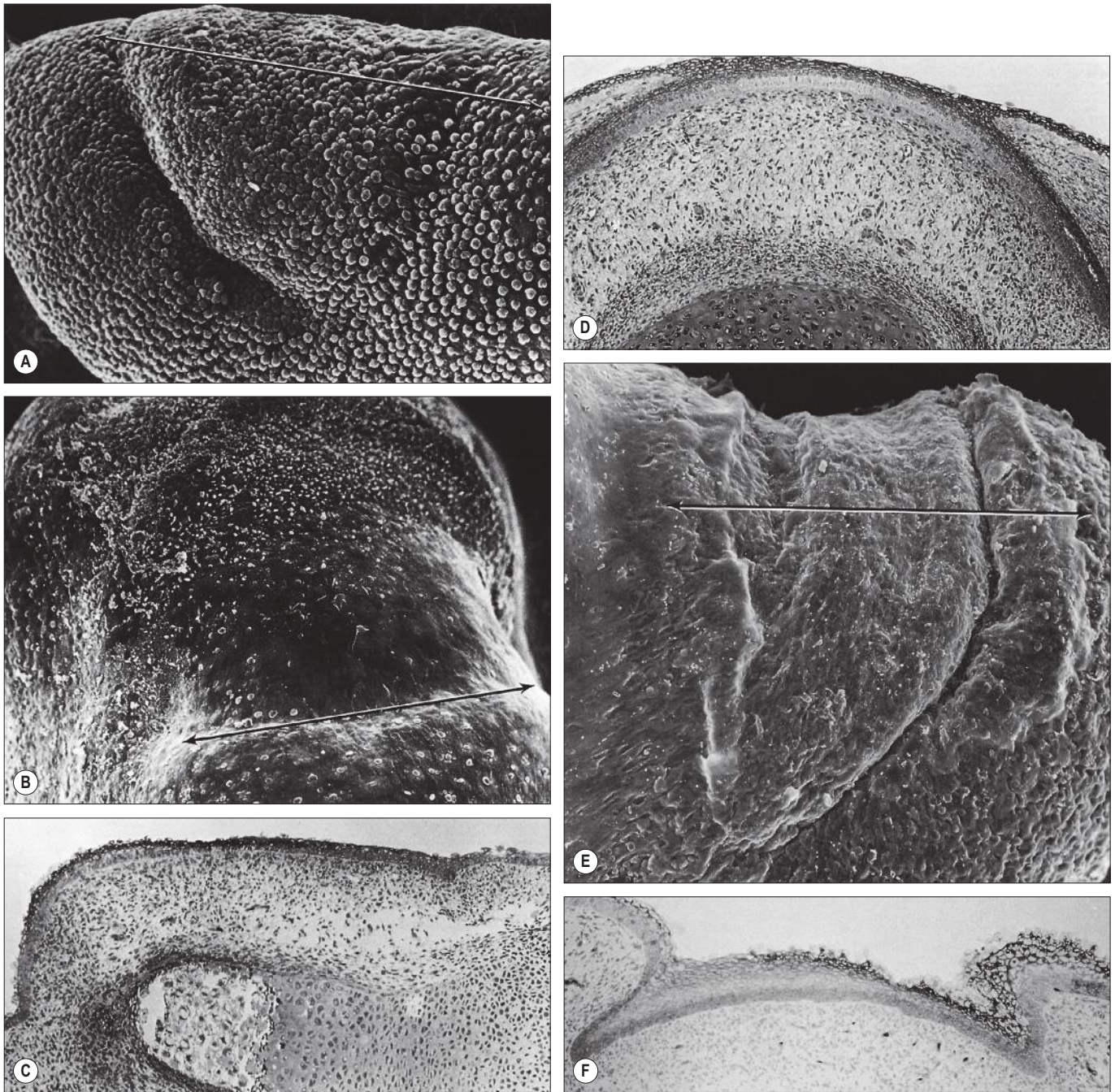


Figure 1.7 Nail development. The developing nail from 65 to 85 days' EGA, by scanning electron and light microscopy. The nail field boundaries are marked by folds seen clearly in A, B, and E. The lines delimited by arrows indicate the plane of the section taken for the accompanying histologic sections. C, D, and F show the increasing thickness and differentiation of the epidermis forming the presumptive nail plate. (Reproduced with permission from Schachner LA, Hansen RC, eds. *Pediatric dermatology*. 2nd ed. Edinburgh: Churchill Livingstone; 1995.)

bed begins to keratinize, a process similar to subsequent keratinization of the embryonic epidermis.^{157–159} In the 4th month, the definitive nail plate grows out distally from the proximal fold, replacing the embryonic cornified layers, and completely covers the nail bed by the 5th month. Keratinization of the nail resembles that of the epidermis except that nail terminal differentiation, like hair shaft differentiation, involves the synthesis of distinct keratins and keratin-aggregating proteins normally not expressed in epidermis.³⁶ The keratins found in hairs and nails provide greater structural stability and rigidity than those in epidermis.

ECCRINE AND APOCRINE SWEAT GLAND DEVELOPMENT

The first morphologic indicators of palmoplantar eccrine gland development are the formation of large mesenchymal bulges or pads on the volar surfaces of the hands and feet between 55 and 65 days' EGA, and the induction of parallel ectodermal ridges overlying these bulges between 12 and 14 weeks (Fig. 1.8).^{160,161} The curves and whorls that these ridges adopt are intimately related to the size and shape of the embryonic volar pads and result in the characteristic dermatoglyphic patterns, or 'finger-prints,' which can be visualized on the surface of the digit tips in the fifth month.^{160,162} In contrast to those of most other animal species, the volar mesenchymal pads in humans regress by the third trimester.

Individual eccrine gland primordia bud at regularly spaced intervals along the ectodermal ridges, elongating as cords of cells into the pad mesenchyme. By 16 weeks, the glandular regions at the terminal portion of this downgrowth have formed, and the secretory and myoepithelial components become discernible. Canalization of the dermal components of the glands occurs by loss of desmosome adhesion along the innermost ectodermal surfaces with maintenance of lateral adhesion between cells of the duct and gland walls. This process is complete by 16 weeks, whereas the opening of the epidermal portion of the duct by vesicular fusion and autolysis and keratinization of the wall are not complete until 22 weeks' EGA.^{163,164} Although the primary ectodermal ridges are established quite early in embryonic development, secondary ridges form at later stages and the complexity of the undulating DEJ increases further at late fetal stages and postnatally with the formation of dermal papillae protruding into the overlying epidermis.

In contrast to volar eccrine glands, interfollicular eccrine glands and apocrine glands do not begin budding until the 5th

month of gestation.^{145,165} Apocrine sweat glands, like sebaceous glands, usually bud from the upper portion of a hair follicle, whereas eccrine sweat glands arise independently. Over the next several weeks, the glandular cords of cells elongate. By 7 months' EGA, the clear cells and mucin-secreting dark cells characteristic of apocrine glands are distinguishable. At birth, the secretory portions of nonvolar sweat glands remain high in the dermis but postnatally extend progressively down to the subcutis. The apocrine gland functions transiently in the third trimester and then becomes quiescent in the neonate,^{166,167} whereas the eccrine gland does not appear to function in utero but progressively reaches functional maturity postnatally.¹⁶⁸

ECTODERMAL APPENDAGES: CLINICAL RELEVANCE

Genetic studies in mice have suggested that mutations in the genes that direct early regional patterning of the mammalian embryo can have a profound impact on later skin appendage specification and differentiation.^{109,110,169,170}

One such gene, *LMX1B*, which encodes a homeobox-containing transcription factor, acts several stages before the initiation of appendageal downgrowths and is important in distal limb patterning.¹⁶⁹ Experimental ablation of *LMX1B* function in mice results in the transformation of dorsal limb musculoskeletal elements and dermal structures to a more ventral (volar side) phenotype. Viewed from the side, *Lmx1b* mutant mouse limbs appear perfectly symmetrical, with the paw pads present on both the ventral and dorsal aspects. Mutations in *LMX1B* have been observed in at least some people with the autosomal dominant disease nail–patella syndrome.¹³³ These patients display a much less dramatic limb phenotype, characterized by aberrant or absent development of the nails and patellae (elbows). This milder effect on dorsal limb structures reflects the fact that individuals with nail–patella syndrome are heterozygotes. Thus, they carry a single defective copy of *LMX1B*, together with a wild-type copy, resulting in only partial loss of gene function.

Several other genes have been identified that appear to regulate skin appendage formation. Positional cloning strategies have been used to identify genes affected in several different types of ectodermal dysplasias, a heterogeneous group of disorders defined by their involvement of hair, nails, glands, and/or teeth. The most common type of ectodermal dysplasia, anhidrotic (hypohidrotic) ectodermal dysplasia, is caused by mutations in the *EDA* or *EDAR* genes, which encode a ligand/receptor pair related to TNF signaling components.¹³⁶ The gene encoding *MSX1*, another homeobox-containing transcription factor, has been shown to be mutated in familial tooth agenesis, which affects not only tooth development but also the formation of nails and hair.^{171,172}

Studies in mice suggest that other classic embryonic patterning genes play a direct role in epidermal appendage development, including genes encoding components of the Notched, Wnt, and Sonic hedgehog signaling pathways.^{130,173} The importance of such genes in human skin homeostasis has already been demonstrated by the finding that *PATCHED* is the tumor suppressor gene mutated in nevoid basal cell carcinoma (Gorlin) syndrome, and that it and other genes of the pathway are frequently mutated in spontaneous basal cell carcinomas.^{174–176} Indeed, several genes involved in tumor formation are critical regulators during embryonic development. Finally, it is

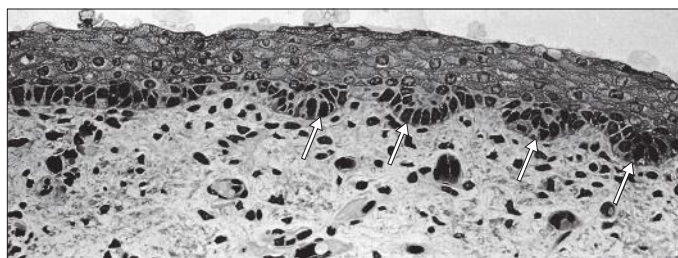


Figure 1.8 Sweat gland development. Plantar epidermis from the digit of a late first-trimester human fetus showing a multilayered epidermis and the primary epidermal ridges (arrows) that will develop into sweat glands and ducts. (Reproduced with permission from Schachner LA, Hansen RC (eds) *Pediatric dermatology*. 2nd ed. Edinburgh: Churchill Livingstone; 1995.)

important to consider potential teratogenic effects on normal skin appendage development. Dilantin, for example, can cause broadening of the nail associated with distortions in the underlying distal phalange.

Clinical paradigms

INNATE IMMUNE FUNCTION

A critical intrauterine function of the skin is the provision of innate immune protection from exogenous infection. Preterm delivery is highly associated with ascending infection from the vaginal vault and subsequent chorioamnionitis. When the infection cannot be confined to the amniotic sac, the fetus responds with a well-coordinated systemic inflammatory response linked to long-term neurological sequelae.^{10,21,22} During the last trimester, increasing levels of pulmonary surfactant are present in the amniotic fluid as measured by lung lamellar body counts.¹⁷⁷ Significantly, analysis of these lamellar bodies show a paucity of contamination with lamellar bodies derived from the epidermis. Vernix caseosa, produced in part by the pilosebaceous apparatus, is present on the skin surface in the last trimester, interacts with pulmonary surfactant with subsequent detachment,¹⁷⁸ and is swallowed by the fetus with potential effects on the developing gut (Fig. 1.9).¹⁷⁹ Pulmonary surfactant and vernix caseosa both contain significant innate immune modulators and provide a first line of defense against microbial invasion of the amniotic fluid.^{10,180}

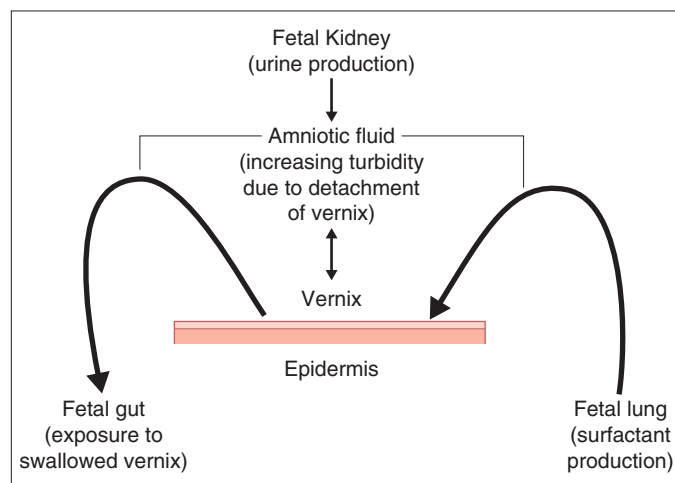


Figure 1.9 Vernix detachment in utero and multiple fetal organ interactions. During the third trimester, the fetal kidney produces copious amounts of urine that contribute to the amniotic fluid volume surrounding the developing fetus. Concomitantly, the fetal lung synthesizes pulmonary surfactant in the form of lamellar bodies that are translocated into the amniotic fluid via the trachea and fetal breathing movements.¹⁷⁷ Sebaceous gland hyperplasia occurs simultaneously with the loss of periderm and the spreading of vernix over the fetal skin surface in association with terminal differentiation of the interfollicular epidermis and formation of the SC. The vernix on the skin surface builds up and detaches into the surrounding milieu resulting in increasing amniotic fluid turbidity. Data indicate a role for pulmonary surfactant to emulsify vernix and aide in the detachment mechanism.¹⁷⁸ Vernix within the amniotic fluid is subsequently swallowed by the fetus with potential effects on the fetal foregut and systemic absorption of vernix components.¹⁷⁹ (Adapted from Hoath SB. *Physiological development of the skin*. In: Polin RA, Fox WW, Abman SH, eds. *Fetal and neonatal physiology*. Philadelphia: Elsevier Saunders; 2011:679–695.)

PRENATAL DIAGNOSIS OF CONGENITAL SKIN DISORDERS

A number of inherited skin disorders are compatible with in utero survival but are life-threatening or result in severe morbidity after birth. Often, these disorders can be diagnosed during the first or second trimesters of pregnancy. Box 1.1 lists a number of diagnostic modalities for detecting skin diseases prenatally. Candidates for prenatal testing include those fetuses with an affected sibling or other family member. Importantly, the need for prenatal testing depends on the familial relationship, the mode of inheritance of the disorder in question, and in some cases, the sex of the fetus. DNA from parents and from both affected and unaffected siblings should be analyzed before conception to determine the exact mutational event responsible for the disorder in the relevant pedigree, and the likelihood that the fetus will in fact inherit the disease.¹⁸⁸ With this in mind, prenatal and genetic counseling should be a critical component of early interventional care of infants affected with severe genodermatoses.¹⁸³

In the past, prenatal diagnosis of inherited disorders often relied on fetal skin biopsies performed between 19 and 22 weeks' EGA.^{23,188} The procedure is carried out under ultrasound guidance, and multiple biopsies must be taken, although the number of biopsies and the sites from which they are taken depend on the disorder for which the fetus is at risk. In some disorders, such as those in which keratinization of the interfollicular dermis is not yet complete, analysis of the developing appendageal structures is required for accurate diagnosis.³¹ Fortunately, because of the identification of the genetic mutations responsible for many of these disorders, diagnosis can be made using cells obtained from CVS at 8–10 weeks' EGA, or amniocentesis at 16–18 weeks' EGA.¹⁸⁴ The obvious advantage of these procedures is that they can be performed early in the pregnancy with minimal risk to the mother and fetus. A parallel development in high technology in obstetrics includes 3D/4D ultrasound imaging, wherein computer reconstruction of real-time images allows an unprecedented view of the body surface and fetal behavior (Fig. 1.10).¹⁸⁹ The spatial resolution of this technique is remarkable,¹⁹⁰ opening the door to a possible 'prenatal dermatology'.

Fundamental knowledge of those skin disorders whose etiologies are genetic, is crucial for the practicing pediatric dermatologist. The number of genodermatoses for which the gene mutation is known increases yearly (Table 1.4). Data on genetic test availability, provided by both commercial and research laboratories, are provided by GeneTest (<http://www.genetests.org>), a database for healthcare providers. Information regarding the identity of genes critical for specific disorders, as well as whether laboratories exist that conduct relevant testing, can also

BOX 1.1 METHODS OF INVESTIGATION OF FETAL SKIN DISEASE

- Genetic counseling of at-risk families^{181,182}
- Preimplantation genetic diagnosis¹⁸³
- Fetal cells and free DNA in maternal blood¹⁸³
- Chorionic villus sampling¹⁸⁴
- Amniocentesis¹⁸⁴
- Fetal skin biopsy²³
- Fetal tissue engineering¹⁸⁵
- 3D/4D ultrasonography^{186,187}

TABLE
1.4

Genodermatoses associated with allelic variations in known genes

Genetic skin disorder	Illustrative disease state or condition	Chapter
Epidermolysis bullosa (EB)	EB simplex variants, junctional EB variants, dystrophic EB variants – recessive and dominant, transient bullous dermolysis of the newborn	10, 11
Disorders of keratinization Ichthyoses	Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome, keratitis-ichthyosis-deafness (KID) syndrome, lamellar ichthyosis, Netherton syndrome, Refsum syndrome, X-linked chondrodysplasia punctata (Conradi-Hunerman syndrome), X-linked recessive ichthyosis	19
Palmoplantar keratodermas	Pachyonychia congenita, striate palmoplantar keratoderma variants, Vohwinkel syndrome variants, Verner syndrome	
Follicular keratosis	Darier-White disease, Hailey-Hailey disease	
Erythrokeratodermias	Erythrokeratoderma variabilis, progressive symmetric erythrokeratoderma	
Disorders with abnormal pigmentation	Chediak-Higashi syndrome, Hermansky-Pudlak syndrome variants, McCune-Albright syndrome, neurofibromatosis variants, oculocutaneous albinism variants, Peutz-Jeghers syndrome, piebaldism, Waardenburg syndrome variants	23, 24
Disorders associated with malignancy	Cowden syndrome, dyskeratosis congenita, Gardner syndrome, nevoid basal cell carcinoma syndrome (Gorlin syndrome), tuberous sclerosis complex, xeroderma pigmentosum	24, 29
Disorders of ectodermal appendages including ectodermal dysplasias	Cartilage hair hypoplasia, familial incontinentia pigmenti, hidrotic and X-linked hypohidrotic ectodermal dysplasias, monilethrix, nail-patella syndrome	29, 32
Connective tissue defects	Cutis laxa, Ehlers-Danlos syndrome and variants, Fabry disease, Marfan syndrome, Menkes kinky hair syndrome, pseudoxanthoma elasticum, Williams syndrome	29, 31
Vascular and lymphatic disorders	Hereditary lymphedema type I, hyperkeratotic cutaneous capillary venous malformations, Osler-Rendu-Weber syndrome, glomerulovenous malformations, venous malformations	20, 21
Porphyrias	Congenital erythropoietic porphyria, erythropoietic protoporphyria (EPP), porphyria cutanea tarda	20
Disorders associated with immunodeficiency	Omenn syndrome, Wiskott-Aldrich syndrome	18
Miscellaneous disorders	Bloom syndrome, Cockayne syndrome, Rothmund Thompson syndrome, hereditary angioedema, Werner syndrome	20, 29

(Adapted from Irvine AD, McLean WH. The molecular genetics of the genodermatoses: progress to date and future directions. *British Journal of Dermatology* 2003; 148:1–13.)



Figure 1.10 3D reconstruction of fetal body surface and facial expression in the third trimester.¹⁸⁶ Recent developments in imaging technology and ultrafast computers allow intrauterine imaging of the skin surface in surprising detail.^{189,190} Real-time (4D) imaging can be utilized to study the relation of the skin surface to reflex development and neurobehavior. (Reproduced with permission from Kurjak A, Miskovic B, Andonotopo W, Stanojevic M, Azumendi G, Vrcic H. How useful is 3D and 4D ultrasound in perinatal medicine? *Journal of Perinatal Medicine* 2007; 35(1):10–27.)

TABLE
1.5

Physical maturity scores used to determine gestational age in premature and term infants

Physical maturity sign	SCORE						
	–1	0	1	2	3	4	5
Skin	Sticky, friable, transparent	Gelatinous, red, translucent	Smooth, pink, visible veins	Superficial peeling and/or rash, few veins	Cracking pale areas, rare veins	Parchment, deep cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40–50 mm: – 1; <40 mm: – 2	>50 mm, no crease	Faint red marks	Anterior transverse crease only	Creases ant. ½	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola, 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/Ear	Lids fused loosely: – 1; tightly: – 2	Lids open, pinna flat, stays folded	Sl. curved pinna; soft; slow recoil	Well-curved pinna; soft but ready recoil	Formed and firm instant recoil	Thick cartilage ear stiff	
Genitals (male)	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals (female)	Clitoris prominent and labia flat	Prominent clitoris and small labia minora	Prominent clitoris and enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

This common bedside tool assigns a score to various physical and neurological criteria, the sum of all of which is then extrapolated to estimate the gestational age of the baby with an effective range of 20–44 weeks (LMP). The scoring relies on the intrauterine changes that the fetus undergoes during its maturation. Whereas the neurological criteria (not shown) depend mainly upon muscle tone, the physical criteria reflect topological skin-based signs.¹⁹²

(Adapted from the scoring system from Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. *Journal of Pediatrics* 1991; 119(3):417–423.)

be accessed through the website for Online Mendelian Inheritance in Man (OMIM), at: <http://www.ncbi.nlm.nih.gov/omim/>.

Gestational age assessment

Throughout this chapter, there has been a conscious effort to highlight the close embryological, physiological, and perceptual-behavioral connections between the skin and the brain. Dermatology and neurology, more than other clinical specialties, place a high priority on the traditional physical examination.¹⁹¹ This focus on the body surface and associated neurobehavior has a parallel in the assessment of gestational age. The commonly used Ballard exam consists of a quantitative bedside evaluation of a set of neurological signs and physical findings, which yield a score commensurate with gestational age between 20 and 40+ weeks' gestation.¹⁹² The physical scores are largely indicative of selected markers of cutaneous development (Table 1.5). The accurate determination of gestational age is important for

organizing care expectations in the newborn nursery and intensive care unit. Subsequent chapters will address the care of the neonate and associated skin disorders of the term and preterm infant.

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Access the full reference list at ExpertConsult.com 

Figures 6 and 7 are available online at ExpertConsult.com 

Tables 1 and 4 are available online at ExpertConsult.com 

KEY REFERENCES

- Hoath SB. Physiological development of the skin. In: Polin RA, Fox WW, Abman SH, editors. *Fetal and neonatal physiology*. Philadelphia: Elsevier Saunders; 2011. p. 679–95.
- Leung A, Crombleholme TM, Keswani SG. Fetal wound healing: implications for minimal scar formation. *Curr Opin Pediatr* 2012;24(3): 371–8.
- Hardman MJ, Moore L, Ferguson MW, et al. Barrier formation in the human fetus is patterned. *J Invest Dermatol* 1999;113(6): 1106–13.
- Holbrook KA, Odland GF. The fine structure of developing human epidermis: light scanning, and transmission electron microscopy of the periderm. *J Invest Dermatol* 1975; 65(1):16–38.
- Moll R, Divo M, Langbein L. The human keratins: biology and pathology. *Histochem Cell Biol* 2008;129(6):705–33.
- Smith LT, Holbrook KA, Byers PH. Structure of the dermal matrix during development and in the adult. *J Invest Dermatol* 1982;79(Suppl 1):93s–104s.
- Williams ML, Hincenbergs M, Holbrook KA. Skin lipid content during early fetal development. *J Invest Dermatol* 1988;91(3):263–8.
- Irvine AD, McLean WH. The molecular genetics of the genodermatoses: progress to date and future directions. *Br J Dermatol* 2003;148(1): 1–13.
- Lai-Cheong JE, Arita K, McGrath JA. Genetic diseases of junctions. *J Invest Dermatol* 2007; 127(12):2713–25.
- Uitto J. Progress in heritable skin diseases: translational implications of mutation analysis and prospects of molecular therapies. *Acta Derm Venereol* 2009;89(3):228–35.

REFERENCES

- Hoath SB. Physiological development of the skin. In: Polin RA, Fox WW, Abman SH, editors. *Fetal and neonatal physiology*. Philadelphia: Elsevier Saunders; 2011. p. 679–95.
- Hooker D. Development reaction to environment. *Yale J Biol Med* 1960;32:431–40.
- Humphrey T. The development of human fetal activity and its relation to postnatal behavior. *Adv Child Dev Behav* 1970;5:1–57.
- Martin DS, Khosravi M, Grocott MP, et al. Concepts in hypoxia reborn. *Crit Care* 2010;14(4):315.
- Leung A, Crombleholme TM, Keswani SG. Fetal wound healing: implications for minimal scar formation. *Curr Opin Pediatr* 2012;24(3):371–8.
- Montagu A. *Touching: the human significance of the skin*. 3rd ed. New York: Perennial Library; 1986.
- Bradley RM, Mistretta CM. Fetal sensory receptors. *Physiol Rev* 1975;55(3):352–82.
- Wakai RT, Lingle JM, Leuthold AC. Transmission of electric and magnetic foetal cardiac signals in a case of ectopia cordis: the dominant role of the vernix caseosa. *Phys Med Biol* 2000;45(7):1989–95.
- Niederborn JY, Wang S. Immune privilege of the eye and fetus: parallel universes? *Transplantation* 2005;80(9):1139–44.
- Hoath SB, Narendran V, Visscher MO. Vernix caseosa and innate immunity. In: Dayan N, Wertz P, editors. *Innate immune system of skin and oral mucosa: properties and impact in pharmaceuticals, cosmetics, and personal care products*. New Jersey: John Wiley; 2011.
- Brazelton T. Behavioral competence. In: Avery G, Fletcher M, MacDonald M, editors. *Neonatology: pathophysiology and management of the newborn*. Philadelphia: JB Lippincott; 1994.
- van der Loos H, Dorfl J. Does the skin tell the somatosensory cortex how to construct a map of the periphery? *Neurosci Lett* 1978;7(1):23–30.
- Morris D. *The naked ape: a zoologist's study of the human animal*. New York: Random House; 1999 (paperback edition).
- Ambalavanan N, Carlo WA, Tyson JE, et al. Outcome trajectories in extremely preterm infants. *Pediatrics* 2012;130(1):e115–25.
- Hardman MJ, Moore L, Ferguson MW, et al. Barrier formation in the human fetus is patterned. *J Invest Dermatol* 1999;113(6):1106–13.
- Madison KC. Barrier function of the skin: 'la raison d'être' of the epidermis. *J Invest Dermatol* 2003;121(2):231–41.
- Schaal B. Mammary odor cues and pheromones: mammalian infant-directed communication about maternal state, mammae, and milk. *Vitam Horm* 2010;83:83–136.
- Schaal B, Marlier L, Soussignan R. Olfactory function in the human fetus: evidence from selective neonatal responsiveness to the odor of amniotic fluid. *Behav Neurosci* 1998;112(6):1438–49.
- Oftedal OT. The evolution of milk secretion and its ancient origins. *Animal* 2012;6(3):355–68.
- Hermansen MC, Hermansen MG. Perinatal infections and cerebral palsy. *Clin Perinatol* 2006;33(2):315–33.
- Levy O. Innate immunity of the newborn: basic mechanisms and clinical correlates. *Nat Rev Immunol* 2007;7(5):379–90.
- Hoath SB, Visscher M, Heaton C, et al. Skin science and the future of dermatology. *J Cutan Med Surg* 1998;3(1):2–8.
- Holbrook KA, Smith LT, Elias S. Prenatal diagnosis of genetic skin disease using fetal skin biopsy samples. *Arch Dermatol* 1993;129(11):1437–54.
- Larsen WL. *Human Embryology*. New York: Churchill Livingstone; 1997.
- Engle WA. Age terminology during the perinatal period. *Pediatrics* 2004;114(5):1362–4.
- Holbrook KA. Structural and biochemical organogenesis of skin and cutaneous appendages in the fetus and newborn. In: Polin RA, Fox WW, editors. *Fetal and neonatal physiology*. Philadelphia: WB Saunders; 1998. p. 729–52.
- Anderson DJ. Stem cells and transcription factors in the development of the mammalian neural crest. *FASEB J* 1994;8(10):707–13.
- Jockusch H, Dress A. From sphere to torus: a topological view of the metazoan body plan. *Bull Math Biol* 2003;65(1):57–65.
- Breathnach AS, Robins J. Ultrastructural features of epidermis of a 14 MM. (6 weeks) human embryo. *Br J Dermatol* 1969;81(7):504–16.
- Holbrook KA, Odland GF. The fine structure of developing human epidermis: light, scanning, and transmission electron microscopy of the periderm. *J Invest Dermatol* 1975;65(1):16–38.
- Holbrook KA, Odland GF. Regional development of the human epidermis in the first trimester embryo and the second trimester fetus (ages related to the timing of amniocentesis and fetal biopsy). *J Invest Dermatol* 1980;74(3):161–8.
- Hertle MD, Adams JC, Watt FM. Integrin expression during human epidermal development in vivo and in vitro. *Development* 1991;112(1):193–206.
- Smith LT, Sakai LY, Burgeson RE, et al. Ontogeny of structural components at the dermal-epidermal junction in human embryonic and fetal skin: the appearance of anchoring fibrils and type VII collagen. *J Invest Dermatol* 1988;90(4):480–5.
- Lourenco SV, Kamibeyppu L, Fernandes JD, et al. Relationship of adhesion molecules expression with epithelial differentiation markers during fetal skin development. *J Cutan Pathol* 2008;35(8):731–7.
- Jackson BW, Grund C, Schmid E, et al. Formation of cytoskeletal elements during mouse embryogenesis. Intermediate filaments of the cytokeratin type and desmosomes in preimplantation embryos. *Differentiation* 1980;17(3):161–79.
- Moll R, Divo M, Langbein L. The human keratins: biology and pathology. *Histochem Cell Biol* 2008;129(6):705–33.
- Hoyes AD. Electron microscopy of the surface layer (periderm) of human foetal skin. *J Anat* 1968;103(Pt 2):321–36.
- Dale BA, Holbrook KA, Kimball JR, et al. Expression of epidermal keratins and filaggrin during human fetal skin development. *J Cell Biol* 1985;101(4):1257–69.
- Moll R, Moll I, Wiest W. Changes in the pattern of cytokeratin polypeptides in epidermis and hair follicles during skin development in human fetuses. *Differentiation* 1982;23(2):170–8.
- Nieland ML, Parmley TH, Woodruff JD. Ultrastructural observations on amniotic fluid cells. *Am J Obstet Gynecol* 1970;108(7):1030–42.
- Lane AT, Helm KF, Goldsmith LA. Identification of bullous pemphigoid, pemphigus, laminin, and anchoring fibril antigens in human fetal skin. *J Invest Dermatol* 1985;84(1):27–30.
- Woodcock-Mitchell J, Eichner R, Nelson WG, et al. Immunolocalization of keratin polypeptides in human epidermis using monoclonal antibodies. *J Cell Biol* 1982;95(2 Pt 1):580–8.
- Bickenbach JR, Holbrook KA. Proliferation of human embryonic and fetal epidermal cells in organ culture. *Am J Anat* 1986;177(1):97–106.
- Bickenbach JR, Holbrook KA. Label-retaining cells in human embryonic and fetal epidermis. *J Invest Dermatol* 1987;88(1):42–6.
- Akiyama M, Smith LT, Yoneda K, et al. Periderm cells form cornified cell envelope in their regression process during human epidermal development. *J Invest Dermatol* 1999;112(6):903–9.
- Weiss RA, Eichner R, Sun TT. Monoclonal antibody analysis of keratin expression in epidermal diseases: a 48- and 56-kdalton keratin as molecular markers for hyperproliferative keratinocytes. *J Cell Biol* 1984;98(4):1397–406.
- Fine JD, Smith LT, Holbrook KA, et al. The appearance of four basement membrane zone antigens in developing human fetal skin. *J Invest Dermatol* 1984;83(1):66–9.
- Muller HK, Kalnins R, Sutherland RC. Ontogeny of pemphigus and bullous pemphigoid antigens in human skin. *Br J Dermatol* 1973;88(5):443–6.
- Smith LT, Holbrook KA, Madri JA. Collagen types I, III, and V in human embryonic and fetal skin. *Am J Anat* 1986;175(4):507–21.
- Hanley K, Rassner U, Elias PM, et al. Epidermal barrier ontogenesis: maturation in serum-free media and acceleration by glucocorticoids and thyroid hormone but not selected growth factors. *J Invest Dermatol* 1996;106(3):404–11.
- Thakorsing VS, Ponc M, Bouwstra JA. Generation of human skin equivalents under submerged conditions-mimicking the in utero environment. *Tissue Eng Part A* 2010;16(4):1433–41.
- Behne MJ, Barry NP, Hanson KM, et al. Neonatal development of the stratum corneum pH gradient: localization and mechanisms leading to emergence of optimal barrier function. *J Invest Dermatol* 2003;120(6):998–1006.
- Behne MJ, Tu CL, Aronchik I, et al. Human keratinocyte ATP2C1 localizes to the Golgi and controls Golgi Ca²⁺ stores. *J Invest Dermatol* 2003;121(4):688–94.
- Holleran WM, Takagi Y, Menon GK, et al. Processing of epidermal glucosylceramides is required for optimal mammalian cutaneous permeability barrier function. *J Clin Invest* 1993;91(4):1656–64.
- Fluhr J, Behne M, Brown BE, et al. Stratum corneum acidification in neonatal skin:

- Secretory phospholipase A2 and the sodium/hydrogen antiporter-1 acidify neonatal rat stratum corneum. *J Invest Dermatol* 2004;122(2):320–9.
56. Fluhr JW, Mao-Qiang M, Brown BE, et al. Functional consequences of a neutral pH in neonatal rat stratum corneum. *J Invest Dermatol* 2004;123(1):140–51.
 57. Elias PM, Goerke J, Friend DS, et al. Freeze-fracture identification of sterol-digitonin complexes in cell and liposome membranes. *J Cell Biol* 1978;78(2):577–96.
 58. Hadji-Rabia S, Baala L, Vabres P, et al. Claudin-1 gene mutations in neonatal sclerosing cholangitis associated with ichthyosis: a tight junction disease. *Gastroenterology* 2004;127(5):1386–90.
 59. De Benedetto A, Rafaels NM, McGirt LY, et al. Tight junction defects in patients with atopic dermatitis. *J Allergy Clin Immunol* 2011;127(3):773–86 e1–7.
 60. Furuse M, Hata M, Furuse K, et al. Claudin-based tight junctions are crucial for the mammalian epidermal barrier: a lesson from claudin-1-deficient mice. *J Cell Biol* 2002;156(6):1099–111.
 61. Turksen K, Troy TC. Permeability barrier dysfunction in transgenic mice overexpressing claudin 6. *Development* 2002;129(7):1775–84.
 62. Huber M, Rettler I, Bernasconi K, et al. Mutations of keratinocyte transglutaminase in lamellar ichthyosis. *Science* 1995;267(5197):525–8.
 63. Laiho E, Ignatius J, Mikkola H, et al. Transglutaminase 1 mutations in autosomal recessive congenital ichthyosis: private and recurrent mutations in an isolated population. *Am J Hum Genet* 1997;61(3):529–38.
 64. Russell LJ, DiGiovanna JJ, Rogers GR, et al. Mutations in the gene for transglutaminase 1 in autosomal recessive lamellar ichthyosis. *Nat Genet* 1995;9(3):279–83.
 65. Novice FM, Collison D, Burgdorf WH. *Handbook of genetic skin disorders*. Philadelphia: WB Saunders; 1994.
 66. Akiyama M, Kim DK, Main DM, et al. Characteristic morphologic abnormality of harlequin ichthyosis detected in amniotic fluid cells. *J Invest Dermatol* 1994;102(2):210–13.
 67. Dale BA, Holbrook KA, Fleckman P, et al. Heterogeneity in harlequin ichthyosis, an inborn error of epidermal keratinization: variable morphology and structural protein expression and a defect in lamellar granules. *J Invest Dermatol* 1990;94(1):6–18.
 68. Milner ME, O'Guin WM, Holbrook KA, et al. Abnormal lamellar granules in harlequin ichthyosis. *J Invest Dermatol* 1992;99(6):824–9.
 69. Evans NJ, Rutter N. Development of the epidermis in the newborn. *Biol Neonate* 1986;49(2):74–80.
 70. Evans NJ, Rutter N. Percutaneous respiration in the newborn infant. *J Pediatr* 1986;108(2):282–6.
 71. Harpin VA, Rutter N. Barrier properties of the newborn infant's skin. *J Pediatr* 1983;102(3):419–25.
 72. Lane AT. Development and care of the premature infant's skin. *Pediatr Dermatol* 1987;4(1):1–5.
 73. Nachman RL, Esterly NB. Increased skin permeability in preterm infants. *J Pediatr* 1971;79(4):628–32.
 74. West DP, Halket JM, Harvey DR, et al. Percutaneous absorption in preterm infants. *Pediatr Dermatol* 1987;4(3):234–7.
 75. Kalia YN, Nonato LB, Lund CH, et al. Development of skin barrier function in premature infants. *J Invest Dermatol* 1998;111(2):320–6.
 76. Loomis CA. Linear hypopigmentation and hyperpigmentation, including mosaicism. *Semin Cutan Med Surg* 1997;16(1):44–53.
 77. Loomis CA. Development and morphogenesis of the skin. *Adv Dermatol* 2001;17:183–210.
 78. Gown AM, Vogel AM, Hoak D, et al. Monoclonal antibodies specific for melanocytic tumors distinguish subpopulations of melanocytes. *Am J Pathol* 1986;123(2):195–203.
 79. Holbrook KA, Underwood RA, Vogel AM, et al. The appearance, density and distribution of melanocytes in human embryonic and fetal skin revealed by the anti-melanoma monoclonal antibody, HMB-45. *Anat Embryol (Berl)* 1989;180(5):443–55.
 80. Breathnach AS, Wyllie LM. Electron microscopy of melanocytes and Langerhans cells in human fetal epidermis at fourteen weeks. *J Invest Dermatol* 1965;44:51–60.
 81. Mishima Y, Widlan S. Embryonic development of melanocytes in human hair and epidermis. Their cellular differentiation and melanogenic activity. *J Invest Dermatol* 1966;46(3):263–77.
 82. Zimmermann AA, Cornbleet T. The development of epidermal pigmentation in the Negro fetus. *J Invest Dermatol* 1948;11(5):383–95.
 83. Foster CA, Holbrook KA, Farr AG. Ontogeny of Langerhans cells in human embryonic and fetal skin: expression of HLA-DR and OKT-6 determinants. *J Invest Dermatol* 1986;86(3):240–3.
 84. Berman B, Chen VL, France DS, et al. Anatomical mapping of epidermal Langerhans cell densities in adults. *Br J Dermatol* 1983;109(5):553–8.
 85. Foster CA, Holbrook KA. Ontogeny of Langerhans cells in human embryonic and fetal skin: cell densities and phenotypic expression relative to epidermal growth. *Am J Anat* 1989;184(2):157–64.
 86. Moll I, Lane AT, Franke WW, et al. Intraepidermal formation of Merkel cells in xenografts of human fetal skin. *J Invest Dermatol* 1990;94(3):359–64.
 87. Moll I, Moll R. Early development of human Merkel cells. *Exp Dermatol* 1992;1(4):180–4.
 88. Saxod R. Ontogeny of the cutaneous sensory organs. *Microsc Res Tech* 1996;34(4):313–33.
 89. Boissy RE, Nordlund JJ. Molecular basis of congenital hypopigmentary disorders in humans: a review. *Pigment Cell Res* 1997;10(1–2):12–24.
 90. Hornyak TJ. The developmental biology of melanocytes and its application to understanding human congenital disorders of pigmentation. *Adv Dermatol* 2006;22:201–18.
 91. Spritz RA. Piebaldism, Waardenburg syndrome, and related disorders of melanocyte development. *Semin Cutan Med Surg* 1997;16(1):15–23.
 92. Rees JL. The genetics of human pigmentary disorders. *J Invest Dermatol* 2011;131(E1):E12–13.
 93. Hogg ID. Sensory nerves and associated structures in the skin of human fetuses of 8 to 14 weeks of menstrual age correlated with functional capability. *J Comp Neurol* 1941;75:371–410.
 94. Humphrey T. The development of trigeminal nerve fibers to the oral mucosa, compared with their development to cutaneous surfaces. *J Comp Neurol* 1966;126(1):91–108.
 95. Cauna N, Mannan G. Organization and development of the preterminal nerve pattern in the palmar digital tissues of man. *J Comp Neurol* 1961;117:309–27.
 96. Cull P. *The sourcebook of medical illustration*. Carnforth: Parthenon; 1989.
 97. Li L, Li Z, Huo HS, et al. Sensory nerve endings in the puborectalis and anal region of the fetus and newborn. *Dis Colon Rectum* 1992;35(6):552–9.
 98. Vega JA, Garcia-Suarez O, Montano JA, et al. The Meissner and Pacinian sensory corpuscles revisited new data from the last decade. *Microsc Res Tech* 2009;72(4):299–309.
 99. Paus R, Theoharides TC, Arck PC. Neuro-immunoendocrine circuitry of the 'brain-skin connection'. *Trends Immunol* 2006;27(1):32–9.
 100. Arck PC, Slominski A, Theoharides TC, et al. Neuroimmunology of stress: skin takes center stage. *J Invest Dermatol* 2006;126(8):1697–704.
 101. Ito N, Ito T, Kromminga A, et al. Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal axis and synthesize cortisol. *FASEB J* 2005;19(10):1332–4.
 102. Narendran V, Visscher MO, Abril I, et al. Biomarkers of epidermal innate immunity in premature and full-term infants. *Pediatr Res* 2010;67(4):382–6.
 103. Michalk A, Stricker S, Becker J, et al. Acetylcholine receptor pathway mutations explain various fetal akinesia deformation sequence disorders. *Am J Hum Genet* 2008;82(2):464–76.
 104. Noden DM. Embryonic origins and assembly of blood vessels. *Am Rev Respir Dis* 1989;140(4):1097–103.
 105. Risau W, Lemmon V. Changes in the vascular extracellular matrix during embryonic vasculogenesis and angiogenesis. *Dev Biol* 1988;125(2):441–50.
 106. Johnson CL, Holbrook KA. Development of human embryonic and fetal dermal vasculature. *J Invest Dermatol* 1989;93(2 Suppl):10S–17S.
 107. Sengal P. *Morphogenesis of the skin*. Cambridge: Cambridge University Press; 1976.
 108. Noden DM. Vertebrate craniofacial development: novel approaches and new dilemmas. *Curr Opin Genet Dev* 1992;2(4):576–81.
 109. Loomis CA, Harris E, Michaud J, et al. The mouse *Engrailed-1* gene and ventral limb patterning. *Nature* 1996;382(6589):360–3.
 110. Parr BA, McMahon AP. Dorsalizing signal Wnt-7a required for normal polarity of D-V and A-P axes of mouse limb. *Nature* 1995;374(6520):350–3.
 111. Smith LT, Holbrook KA. Development of dermal connective tissue in human embryonic and fetal skin. *Scan Electron Microsc* 1982; (Pt 4):1745–51.
 112. Holbrook KA. Structure and function of the developing human skin. In: Goldsmith LA, editor. *Physiology, biochemistry, and molecular biology of the skin*. New York: Oxford Press; 1991. p. 63–110.
 113. Epstein EH Jr. (Alpha1(3))3 human skin collagen. Release by pepsin digestion and preponderance in fetal life. *J Biol Chem* 1974;249(10):3225–31.
 114. Sykes B, Puddle B, Francis M, et al. The estimation of two collagens from human dermis by interrupted gel electrophoresis. *Biochem Biophys Res Commun* 1976;72(4):1472–80.

115. Deutsch TA, Esterly NB. Elastic fibers in fetal dermis. *J Invest Dermatol* 1975;65(3):320–3.
116. Cass DL, Bullard KM, Sylvester KG, et al. Wound size and gestational age modulate scar formation in fetal wound repair. *J Pediatr Surg* 1997;32(3):411–15.
117. Coolen NA, Schouten KC, Middelkoop E, et al. Comparison between human fetal and adult skin. *Arch Dermatol Res* 2010;302(1):47–55.
118. Holbrook KA, Dale BA, Witt DR, et al. Arrested epidermal morphogenesis in three newborn infants with a fatal genetic disorder (restrictive dermopathy). *J Invest Dermatol* 1987;88(3):330–9.
119. Mau U, Kendziorra H, Kaiser P, et al. Restrictive dermopathy: report and review. *Am J Med Genet* 1997;71(2):179–85.
120. Mucke J, Happle R, Theile H. MIDAS syndrome respectively MLS syndrome: a separate entity rather than a particular lyonization pattern of the gene causing Goltz syndrome. *Am J Med Genet* 1995;57(1):117–18.
121. Happle R. Lyonization and the lines of Blaschko. *Hum Genet* 1985;70(3):200–6.
122. Wang X, Reid Sutton V, Omar Peraza-Llanes J, et al. Mutations in X-linked PORCN, a putative regulator of Wnt signaling, cause focal dermal hypoplasia. *Nat Genet* 2007;39(7):836–8.
123. Smith LT, Holbrook KA, Byers PH. Structure of the dermal matrix during development and in the adult. *J Invest Dermatol* 1982;79(Suppl 1):93s–104s.
124. Fujita H, Asagami C, Oda Y, et al. Electron microscopic studies of the differentiation of fat cells in human fetal skin. *J Invest Dermatol* 1969;53(2):122–39.
125. Poulos SP, Hausman DB, Hausman GJ. The development and endocrine functions of adipose tissue. *Mol Cell Endocrinol* 2010;323(1):20–34.
126. Lane AT. Human fetal skin development. *Pediatr Dermatol* 1986;3(6):487–91.
127. Riddle CV. Focal tight junctions between mesenchymal cells of fetal dermis. *Anat Rec* 1986;214(2):113–17.
128. Christiano AM, Uitto J. Molecular complexity of the cutaneous basement membrane zone. Revelations from the paradigms of epidermolysis bullosa. *Exp Dermatol* 1996;5(1):1–11.
129. Hardy MH. The secret life of the hair follicle. *Trends Genet* 1992;8(2):55–61.
130. Oro AE, Scott MP. Splitting hairs: dissecting roles of signaling systems in epidermal development. *Cell* 1998;95(5):575–8.
131. Sundberg JP. Handbook of mouse mutations with skin and hair abnormalities: Animal models and biomedical tools. Boca Raton: CRC Press; 1994.
132. Ahmad W, Faiyaz ul Haque M, Brancolini V, et al. Alopecia universalis associated with a mutation in the human hairless gene. *Science* 1998;279(5351):720–4.
133. Dreyer SD, Zhou G, Baldini A, et al. Mutations in LMX1B cause abnormal skeletal patterning and renal dysplasia in nail patella syndrome. *Nat Genet* 1998;19(1):47–50.
134. Ferguson BM, Brockdorff N, Formstone E, et al. Cloning of Tabby, the murine homolog of the human EDA gene: evidence for a membrane-associated protein with a short collagenous domain. *Hum Mol Genet* 1997;6(9):1589–94.
135. Srivastava AK, Pispas J, Hartung AJ, et al. The Tabby phenotype is caused by mutation in a mouse homologue of the EDA gene that reveals novel mouse and human exons and encodes a protein (ectodysplasin-A) with collagenous domains. *Proc Natl Acad Sci U S A* 1997;94(24):13069–74.
136. Kere J, Srivastava AK, Montonen O, et al. X-linked anhidrotic (hypohidrotic) ectodermal dysplasia is caused by mutation in a novel transmembrane protein. *Nat Genet* 1996;13(4):409–16.
137. Holbrook KA, Odland GF. Structure of the human fetal hair canal and initial hair eruption. *J Invest Dermatol* 1978;71(6):385–90.
138. Pinkus H. Embryology of hair. In: Montagna W, Ellis RA, editors. *The biology of hair growth*. New York: Academic Press; 1958. p. 1–32.
139. Carlsen RA. Human fetal hair follicles: the mesenchymal component. *J Invest Dermatol* 1974;63(2):206–11.
140. Hashimoto K. The ultrastructure of the skin of human embryos. V. The hair germ and perifollicular mesenchymal cells. *Hair germ-mesenchyme interaction*. *Br J Dermatol* 1970;83(1):167–76.
141. Breathnach AS, Smith J. Fine structure of the early hair germ and dermal papilla in the human foetus. *J Anat* 1968;102(Pt 3):511–26.
142. Robins EJ, Breathnach AS. Fine structure of the human foetal hair follicle at hair-peg and early bulbous-peg stages of development. *J Anat* 1969;104(Pt 3):553–69.
143. Lavker RM, Sun TT, Oshima H, et al. Hair follicle stem cells. *J Invest Dermatol* 2003;8(1):28–38.
144. Montagna W, Van Scott E. The anatomy of the hair follicle. In: Montagna W, Ellis RA, editors. *The biology of hair growth*. New York: Academic Press; 1958. p. 39–64.
145. Serri F, Montagna W, Mescon H. Studies of the skin of the fetus and the child. II. Glycogen and amylophosphorylase in the skin of the fetus. *J Invest Dermatol* 1962;39:199–217.
146. Smith DW, Gong BT. Scalp hair patterning: its origin and significance relative to early brain and upper facial development. *Teratology* 1974;9(1):17–34.
147. Barth JH. Normal hair growth in children. *Pediatr Dermatol* 1987;4(3):173–84.
148. Paus R. Principles of hair cycle control. *J Dermatol* 1998;25(12):793–802.
149. Serri F, Huber MW. The development of sebaceous glands in man. In: Montagna W, Ellis RA, Silver AF, editors. *Advances in biology of skin*. The sebaceous glands. Oxford: Pergamon; 1963. p. 1–18.
150. Fujita H, Asagami C, Murota S, et al. Ultrastructural study of embryonic sebaceous cells, especially of their sebum droplet formation. *Acta Derm Venereol* 1972;52(2):99–115.
151. Williams ML, Hincenbergs M, Holbrook KA. Skin lipid content during early fetal development. *J Invest Dermatol* 1988;91(3):263–8.
152. Pochi PE, Strauss JS, Downing DT. Age-related changes in sebaceous gland activity. *J Invest Dermatol* 1979;73(1):108–11.
153. Zouboulis CC, Baron JM, Bohm M, et al. Frontiers in sebaceous gland biology and pathology. *Exp Dermatol* 2008;17(6):542–51.
154. Zouboulis CC, Fimmel S, Ortmann J, et al. Sebaceous glands. In: Hoath SB, Maibach HI, editors. *Neonatal skin: structure and function*. 2nd ed. New York: Marcel Dekker; 2003. p. 59–88.
155. Rissmann R, Groenink HW, Weerheim AM, et al. New insights into ultrastructure, lipid composition and organization of vernix caseosa. *J Invest Dermatol* 2006;126(8):1823–33.
156. Holbrook KA. Structural abnormalities of the epidermally derived appendages in skin from patients with ectodermal dysplasias: insight into developmental errors. In: Salinas C, editor. *The ectodermal dysplasias, birth defects: original article series*. New York: Liss; 1988. p. 15–44.
157. Hashimoto K, Gross BG, Nelson R, et al. The ultrastructure of the skin of human embryos. 3. The formation of the nail in 16–18 weeks old embryos. *J Invest Dermatol* 1966;47(3):205–17.
158. Lewis BL. Microscopic studies of fetal and mature nail and surrounding soft tissue. *AMA Arch Derm Syphilol* 1954;70(6):733–47.
159. Zaia N. Embryology of the human nail. *Arch Dermatol* 1963;87:37–53.
160. Hirsch W, Schweichel JU. Morphological evidence concerning the problem of skin ridge formation. *J Ment Defic Res* 1973;17(1):58–72.
161. Mulvihill JJ, Smith DW. The genesis of dermatoglyphics. *J Pediatr* 1969;75(4):579–89.
162. Okajima M. Development of dermal ridges in the fetus. *J Med Genet* 1975;12(3):243–50.
163. Hashimoto K. Demonstration of the intercellular spaces of the human eccrine sweat gland by lanthanum. II. The duct. *J Ultrastruct Res* 1971;37(5):504–20.
164. Hashimoto K, Gross BG, Lever WF. The ultrastructure of the skin of human embryos. I. The intraepidermal eccrine sweat duct. *J Invest Dermatol* 1965;45(3):139–51.
165. Hashimoto K. The ultrastructure of the skin of human embryos. VII. Formation of the apocrine gland. *Acta Derm Venereol* 1970;50(4):241–51.
166. Montagna W, Parakkal PF. Apocrine glands. In: Montagna W, Parakkal PF, editors. *The structure and function of skin*. New York: Academic Press; 1974. p. 332–65.
167. Solomon LM, Esterly NB. Neonatal dermatology. I. The newborn skin. *J Pediatr* 1970;77(5):888–94.
168. Sinclair JC. Thermal control in premature infants. *Annu Rev Med* 1972;23:129–48.
169. Chen H, Lun Y, Ovchinnikov D, et al. Limb and kidney defects in Lmx1b mutant mice suggest an involvement of LMX1B in human nail patella syndrome. *Nat Genet* 1998;19(1):51–5.
170. Loomis CA, Kimmel RA, Tong CX, et al. Analysis of the genetic pathway leading to formation of ectopic apical ectodermal ridges in mouse Engrailed-1 mutant limbs. *Development* 1998;125(6):1137–48.
171. Lyngstadaas SP, Nordbo H, Gedde-Dahl T, et al. On the genetics of hypodontia and microdontia: synergism or allelism of major genes in a family with six affected members. *J Med Genet* 1996;33(2):137–42.
172. Vastardis H, Karimbux N, Guthua SW, et al. A human MSX1 homeodomain missense mutation causes selective tooth agenesis. *Nat Genet* 1996;13(4):417–21.
173. Chuong C-M. Molecular basis of epithelial appendage morphogenesis. Austin: RG Landes; 1998.
174. Aszterbaum M, Rothman A, Johnson RL, et al. Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. *J Invest Dermatol* 1998;110(6):885–8.
175. Johnson RL, Rothman AL, Xie J, et al. Human homolog of patched, a candidate gene for the

- basal cell nevus syndrome. *Science* 1996; 272(5268):1668–71.
176. Xie J, Murone M, Luoh SM, et al. Activating Smoothed mutations in sporadic basal-cell carcinoma. *Nature* 1998;391(6662):90–2.
 177. Ridsdale R, Lewis DF, Weaver TE, et al. Proteomic analysis of lamellar bodies isolated from amniotic fluid: implications for function. *Am J Perinatol* 2012;29(6):419–28.
 178. Narendran V, Wickett RR, Pickens WL, et al. Interaction between pulmonary surfactant and vernix: a potential mechanism for induction of amniotic fluid turbidity. *Pediatr Res* 2000; 48(1):120–4.
 179. Ran-Ressler RR, Devapatla S, Lawrence P, et al. Branched chain fatty acids are constituents of the normal healthy newborn gastrointestinal tract. *Pediatr Res* 2008;64(6):605–9.
 180. Akinbi HT, Narendran V, Pass AK, et al. Host defense proteins in vernix caseosa and amniotic fluid. *Am J Obstet Gynecol* 2004;191(6): 2090–6.
 181. Irvine AD, McLean WH. The molecular genetics of the genodermatoses: progress to date and future directions. *Br J Dermatol* 2003;148(1): 1–13.
 182. Lai-Cheong JE, Arita K, McGrath JA. Genetic diseases of junctions. *J Invest Dermatol* 2007; 127(12):2713–25.
 183. Uitto J. Progress in heritable skin diseases: translational implications of mutation analysis and prospects of molecular therapies. *Acta Derm Venereol* 2009;89(3):228–35.
 184. Collins SL, Impey L. Prenatal diagnosis: types and techniques. *Early Hum Dev* 2012;88(1): 3–8.
 185. Fauza DO, Fishman SJ, Mehegan K, et al. Videofetoscopically assisted fetal tissue engineering: skin replacement. *J Pediatr Surg* 1998; 33(2):357–61.
 186. Kurjak A, Miskovic B, Andonotopo W, et al. How useful is 3D and 4D ultrasound in perinatal medicine? *J Perinat Med* 2007;35(1): 10–27.
 187. Avni FE, Cos T, Cassart M, et al. Evolution of fetal ultrasonography. *Eur Radiol* 2007;17(2): 419–31.
 188. Sybert VP, Holbrook KA. Prenatal diagnosis and screening. *Dermatol Clin* 1987;5(1): 17–41.
 189. Basgul AY, Kavak ZN, Guducu N, et al. Prenatal diagnosis of congenital harlequin ichthyosis with 2D, 3D, and 4D ultrasonography. *Clin Exp Obstet Gynecol* 2011;38(3):283–5.
 190. Bord A, Valsky DV, Yagel S. Prenatal sonographic diagnosis of congenital perineal skin tag: case report and review of the literature. *Prenat Diagn* 2006;26(11):1065–7.
 191. Kugler J, Verghese A. The physical exam and other forms of fiction. *J Gen Intern Med* 2010; 25(8):756–7.
 192. Ballard JL, Khoury JC, Wedig K, et al. New Ballard Score, expanded to include extremely premature infants. *J Pediatr* 1991;119(3): 417–23.

Structure and Function of Newborn Skin

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Introduction

The skin of the newborn serves a pivotal role in the transition from the aqueous intrauterine environment to extrauterine terrestrial life and is integral to the vital functions of mechanical protection, thermoregulation, cutaneous immunosurveillance, and maintenance of a barrier that prevents insensible loss of body fluids. The anatomy and function of skin are most easily understood by dissecting the individual compartments (stratum corneum, epidermis, dermoepidermal junction (DEJ), dermis and subcutaneous tissue) and their component cell types. Specialized structures found within these compartments, such as pilosebaceous units, sweat glands, nerves, and vascular networks, play an essential role both anatomically and functionally in cutaneous homeostasis in the neonate. The anatomy of these compartments and structures of the skin, and the physiologic processes involved in their functions, are the focus of this chapter.

Human skin consists of three layers: epidermis, dermis, and subcutaneous fat (Fig. 2.1). All elements of skin are derived from either ectoderm or mesoderm, the former giving rise to the epidermis and other cutaneous epithelial components.¹ A brief description of fetal skin development is helpful in understanding the structure and function of newborn skin, and is incorporated into some of the following discussions of the various compartments and structures. A more thorough review of cutaneous embryology is the focus of Chapter 1.

Stratum corneum and epidermis

The most obvious clinical difference between the skin of the term newborn and that of an adult is the presence of the moist, greasy, yellow-white substance called *vernix caseosa*, which is a coating comprised of a combination of sebaceous gland secretions, desquamated skin cells, and shed lanugo hairs.^{2,3} The vernix caseosa has an important role in maintaining hydration and pH balance, and preventing infection during the first few days of life.^{4,5} Certain components of the innate immune system, termed antimicrobial polypeptides (see ‘Cutaneous immunosurveillance, Langerhans’ cells, and cytokines’, below), have been isolated in the vernix and probably play an important role in surface defense in the newborn.^{4,6,7} This coating persists for the first several days of postnatal life, eventually disappearing completely to reveal the more typical, moderately dry newborn skin. Vernix provides water-binding free amino acids, which may help to facilitate the neonate’s adaptation from the amniotic fluid intrauterine milieu to the ambient dryness of the extrauterine environment.⁸ Vernix-based topical creams have been investigated for treatment of epidermal wounds and augmentation of barrier repair in infants.⁹

The structure of term newborn skin is histologically similar to that of older individuals, whereas premature infant skin reveals several unique features that have increased our understanding of fetal skin development. The outermost compartment of the skin, the epidermis, arises from surface ectoderm and at about the 3rd week of fetal life, consists of a single layer of undifferentiated cells that becomes two-layered by around 4 weeks.¹⁰ The outer layer of cells, the periderm, is found only in developing skin and is transiently present, eventually undergoing a series of apoptotic cellular events as the epidermis becomes multilayered and the stratum corneum, the outermost layer of flattened, non-nucleated skin cells, is forming.¹¹ By 24 weeks’ gestation, the periderm is largely absent,^{10,11} and the epidermis shows considerable progressive maturation, which is largely complete by 34 weeks.¹² A thin, hydrophobic layer of the periderm may persist for several days postnatally and may participate in protective and thermoregulatory functions.¹³

The epidermis is a stratified epithelium, the number of cell layers varying between different body regions. The various layers, from the dermal side toward the skin surface, are termed the stratum basale, stratum spinosum, stratum granulosum, and stratum corneum. In areas of thicker skin, such as the palms and soles, the stratum lucidum is interposed between the granular and corneal layers. These epidermal layers are shown in Figure 2.2.

Individual cells within the epidermis are referred to as *keratinocytes*, so named for the intermediate-sized filament proteins (keratins) that are synthesized within them. Keratins (K) are the major structural proteins of the epidermis and its appendages, constituting up to 85% of the total protein of fully differentiated epidermal keratinocytes.¹⁴ They have been divided into types I and II based on their acidic or basic nature, respectively, and are frequently configured in specific pairs of a type I and a type II protein as obligatory heteropolymers.¹⁵ Terminal differentiation of the epidermis involves the sequential expression of different proteins, including the keratins, in the basal and spinal layers.¹⁶ An important function of the keratins is imparting mechanical integrity to epithelial cells. Mutations in the genes encoding these proteins have been confirmed as the basis of several inherited skin defects, such as the simplex form of the mechanobullosus disease, epidermolysis bullosa.¹⁴ The profiles of epithelial cell keratins change during gestation: K5 and K14 (basal cell keratins) are present from 8 weeks’ gestation, K1 and K10 (differentiation-specific keratins) begin to be expressed between 9 and 10 weeks’ gestation, and some keratins (such as K8 and K19) are present in the fetus but not in adult epidermis.¹⁷

The stratum basale consists of a single layer of cells, the basal portions of which are in contact with the dermis and contribute to the DEJ. The cells of the basal layer are cuboidal to columnar in shape and are anchored to the underlying dermis by

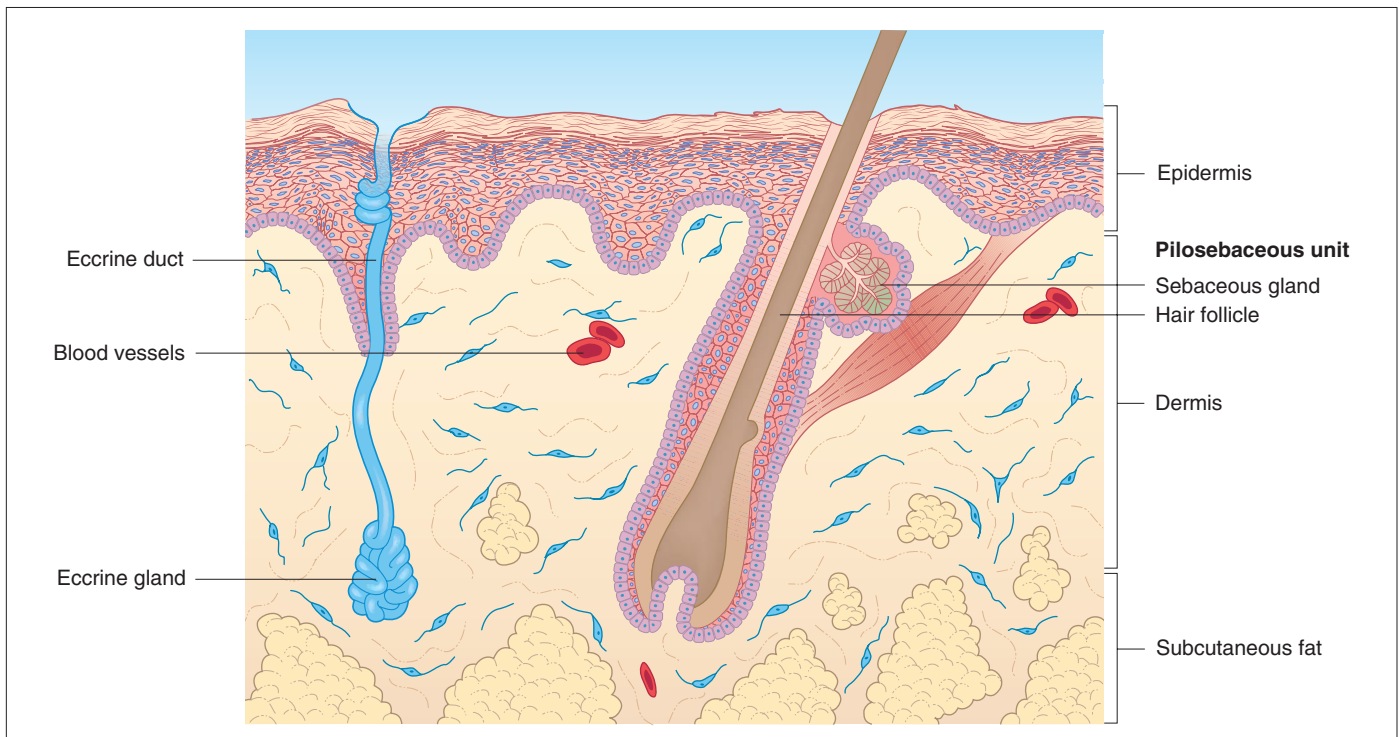


Figure 2.1 Basic anatomy of the skin, which is composed of three major divisions: epidermis, dermis, and subcutaneous fat. Adnexal structures include pilosebaceous units and eccrine ducts and glands (shown), and apocrine glands (not shown). (Courtesy of Randall Hayes.)

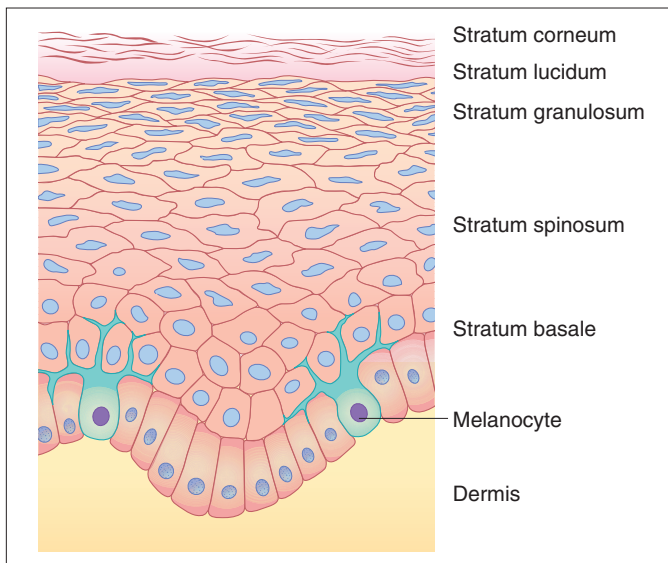


Figure 2.2 The cell layers of the epidermis. Note the interspersed distribution of melanocytes in the basal cell layer. (Courtesy of Randall Hayes.)

cytoplasmic processes. The stratum basale has an undulating surface inferiorly, forming projections called rete ridges, which lie interposed between the dermal papillae of the superficial (papillary) dermis (Fig. 2.3). The basal cell layer contains cells that eventually replace those continually lost from the epidermis through terminal differentiation, maturation and desquamation. Interspersed among the cells in the basal cell layer are the dendritic, pigment (or melanin)-producing cells (melanocytes), which are discussed in more detail below ('Melanocytes and pigmentation of the skin').

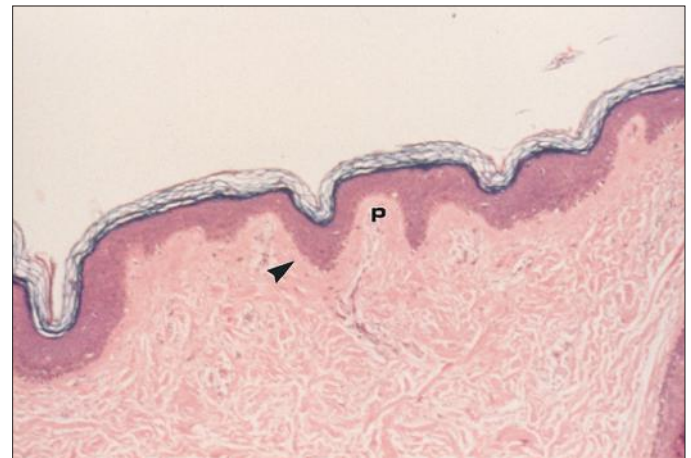


Figure 2.3 Histologic appearance of normal skin. The basal portion of the epidermis has an undulating surface, resulting in rete ridges (arrowhead) interposed between dermal papillae (P).

The stratum spinosum consists of the cells between the stratum basale and the stratum granulosum and forms the bulk of mammalian epidermis. The keratinocytes in this layer are polyhedral in shape and have numerous tiny, spiny projections spanning the intercellular space between contiguous cells.¹⁸ These projections are composed ultrastructurally of desmosomes, which form communication junctions between the cells. Keratinocytes of the spinous layer become larger, flatter, and more desiccated as they progress from the basal layer toward the skin surface. Also present in this layer are Langerhans' cells, bone marrow-derived cells that are involved in cutaneous immunosurveillance through antigen processing and presentation

(see 'Cutaneous immunosurveillance, Langerhans' cells and cytokines', below).

The stratum granulosum comprises a thin layer of darkly stained keratinocytes at the outermost surface of the stratum spinosum. The dark appearance of these cells is due to the presence of keratohyalin granules, which are composed of an electron-dense protein (profilaggrin) and keratin intermediate filaments.¹⁹ Profilaggrin is subsequently converted to filaggrin, a protein involved in the aggregation and disulfide bonding of keratin filaments,^{20,21} and it has been suggested that keratohyalin serves to form a matrix that provides structural support by linking keratin filaments to one another.¹⁸ Filaggrin eventually is degraded into free amino acids, including histidine and glutamine, which are further metabolized into urocanic acid (UCA) and 2-pyrrolidone-5-carboxylic acid (PCA). These free amino acids and their by-products constitute a significant component of natural moisturizing factor (NMF), which is retained in non-nucleated keratinized cells (corneocytes) and helps maintain epidermal hydration.²² The granular cell layer is also where lamellar bodies (lamellar granules, Odland bodies, membrane-coating granules) are produced.²³ These intracellular organelles participate in the formation of the epidermal permeability barrier through the production and discharge of lipid substances into the intercellular corridors of the stratum corneum. Defective lipid transport in lamellar bodies caused by mutations in *ABCA12* underlies the severe skin disorder known as harlequin ichthyosis.²⁴ In areas of thicker skin, such as the palms and soles, the stratum lucidum is present as a layer with a clear hyaline appearance. At this level one can visualize transitional cells that exhibit marked degeneration of the nucleus and other organelles and, ultramicroscopically, keratin filaments and keratohyalin granules, which are abundant but not yet as compact as in the stratum corneum.¹⁸

The stratum corneum, or cornified layer, is composed of several layers of flattened corneocytes arranged in an overlapping fashion. The thickness of this layer varies by body region, being thinnest on the face (especially over the eyelids) and genitalia, and thickest on the palms and soles. It is now widely accepted that the epidermal permeability barrier resides in the stratum corneum and serves the vital functions of preventing excessive transepidermal water loss (TEWL) and preventing penetration of a variety of substances.^{25–29}

The formation of the epidermal barrier is accomplished through the lipid secretions of lamellar bodies, which include free fatty acids, ceramides, and cholesterol. These lipids are deposited in the intercellular interstices within the stratum corneum. This arrangement has been likened to 'bricks and mortar,' where the corneocytes represent the bricks and the intercellular lipids represent the mortar.³⁰ Although these lipids represent only about 10% of the dry weight of the stratum corneum,³¹ their location and composition are vital, and cutaneous barrier function is dependent on both the generation of sufficient quantities of these lipids and their strategic secretion and organization into lamellar bilayer unit structures.^{29,30,32–34} In fact, the epidermis is equipped with the necessary machinery to autonomously regulate its lipid-synthesis apparatus in response to specific barrier requirements.^{35–37} The development of a functional barrier has been shown to be closely correlated with normal ontogenesis and does not appear to be disrupted by somatic growth retardation.³⁸ Hence, more mature infants, even those who are small for gestational age, have a competent epidermal barrier.³⁹

The epidermis and stratum corneum in the full-term infant are well developed, and the barrier properties are excellent.⁴⁰ Conversely, premature infants have greater skin permeability and a more poorly functioning barrier. Histologically, the term infant has a well-developed epidermis, which is several layers thick, and a well-formed stratum corneum.^{2,12} This maturity is lacking in preterm infants.^{40–44} An acceleration of skin maturation may occur postnatally in preterm infants, although in extremely low-birthweight infants (23–25 weeks' gestational age), complete development of a fully functional barrier may require up to 8 weeks.^{41,42,45} Studies support the long-held notion that the shift from an aqueous to an air environment, and hence water flux, may be an important factor in this acceleration of barrier formation.⁴⁶ The nuclear hormone receptors peroxisome proliferator-activated receptor (PPAR- α , - δ , - γ) and their ligands have varied roles in driving the development of the stratum corneum and permeability barrier in the fetus as well as in neonates and adults.⁴⁷ Functional skin adaptation is an ongoing dynamic process involving acidification, water management and permeability barrier development throughout the first year of life and perhaps beyond. The ability to restore the epidermal barrier declines in adulthood.^{48,49} During the period of postnatal barrier maturation, large transepidermal water losses contribute to the morbidity of the preterm infant, and therefore a major focus of past studies has been the development of a therapeutic strategy to accelerate epidermal barrier maturation or augment its function, including the use of semipermeable membranes^{50–53} or topical emollients.^{54,55} Skin surface pH is another important consideration, as acidification is vital to epidermal barrier maturation, and the 'acid mantle' also plays a role in maintaining bacterial and chemical resistance of the skin. While no definitive relationship between gestational age and skin pH has been confirmed, studies have shown that skin pH is higher (more alkaline) immediately after birth, and decreases (becomes more acidic) over the first few weeks of postnatal life.⁵⁶ Premature infant skin and barrier maturation are discussed in more detail in [Chapter 4](#).

In addition to the prevention of insensible water losses across the skin by the epidermal barrier, the epidermis and stratum corneum of the newborn provide important protection against toxicity from exposure to ultraviolet rays (UVR), and this protective effect may be greater for UVB than for UVA radiation.⁵⁷ As previously noted, melanin is primarily responsible for UVR protection, although the 'protein barrier' of the stratum corneum may augment this cutaneous function.⁵⁸ Epidermal lipids may also play a role in protection from UVR. Another function of the superficial skin layers is protection against microorganisms, which are blocked from invasion across the skin by an intact stratum corneum. In addition to such physical factors, the antimicrobial qualities of skin may be related to the relative dryness of the stratum corneum, the presence of skin surface lipids, and the degree of epidermal cellular differentiation.^{58–61} Skin is also a vital participant in the process of neonatal thermoregulation (discussed in more detail later) through regulation of cutaneous blood flow and evaporative water loss.

Percutaneous absorption of substances across neonatal skin requires passage through the stratum corneum and epidermis, diffusion into the dermis, and eventual transfer into the systemic circulation. Transfer across the stratum corneum and epidermis may be through the intercellular corridors (favoring nonpolar or hydrophobic compounds) or via a transcellular

route (which favors polar or hydrophilic substances).⁶² Hair follicles and eccrine sweat ducts may serve as diffusion shunts for certain substances (i.e. ions, polar compounds, very large molecules), which would otherwise traverse the stratum corneum slowly (because of their large molecular weight).⁶³ The rate-limiting step of percutaneous absorption seems to be diffusion through the stratum corneum,⁶³ and hence the effectiveness of the epidermal permeability barrier correlates inversely with percutaneous absorption. Percutaneous absorption, although continuously being explored for therapeutic applications, may contribute to systemic absorption and potential toxicity after topical application of some substances to newborn skin, especially in preterm infants or those with cutaneous damage.⁴¹ Importantly, although the barrier function of intact skin in the term infant is usually normal, the surface area-to-weight ratio is greater than in older children and adults. Caution should therefore be exercised in the use of topical agents in any newborn, with extra caution and a thorough risk–benefit analysis being employed in the case of premature infants or any neonate with a compromised skin barrier. Percutaneous absorption is discussed in more detail in Chapter 5.

Dermoepidermal junction

The dermoepidermal junction (DEJ) is an important site of attachment in skin, occurring at the interface between the basal epidermis and the papillary dermis. It appears that the various components of the DEJ are expressed in term newborn skin in a manner similar to that in adults, without apparent differences in their quantity or associations.² For reasons that are poorly understood, however, skin appears to be more fragile during the newborn period, even in term infants, as evidenced by blisters or erosions developing in situations that do not cause blisters later in life (e.g., erosions due to diapering, sucking blisters on fingers and hands, and disease states such as bullous syphilis).

Specialized structures called ‘hemidesmosomes’ assist in anchoring the basal keratinocytes to the underlying plasma membrane. Ultrastructurally, the DEJ can be broken down into several planes, including (from the epidermal side to the dermal side) the inferior portion of the basal keratinocyte; an empty-appearing, electron-lucent clear plane known as the lamina lucida; a thin, dark, electron-dense layer known as the lamina densa; and the sublamina densa fibrillar region (Fig. 2.4).^{19,64} Each of these layers contains individual components that function harmoniously in concert to create cohesion between the epidermis and the underlying dermis. Defects in, or antibodies directed against, some of these components have been etiologically linked to cutaneous disease.

Major constituents of the DEJ include bullous pemphigoid (BP) antigens, $\alpha 6 \beta 4$ integrin, laminin-5 (laminin-332), type IV collagen, and type VII collagen. The BP antigens are large glycoproteins with both intracellular (BP antigen 1) and transmembrane (BP antigen 2) components. BP antigen 2, also known as collagen type XVII, extends from the basal keratinocyte across the lamina lucida into the lamina densa,⁶⁵ and autoantibodies directed against it have been found in the sera of patients with BP, pemphigoid gestationis, mucous membrane pemphigoid, linear IgA disease, lichen planus pemphigoides, and pemphigoid nodularis.^{66,67} Reduced or absent expression of BP antigen 2 is found in patients with a hereditary junctional form of epidermolysis bullosa (EB) termed

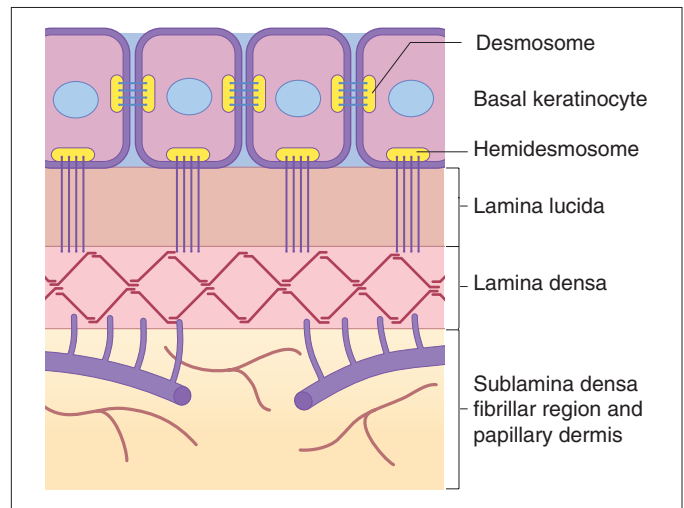


Figure 2.4 Depiction of the ultrastructure of the dermoepidermal junction (DEJ). Hemidesmosomes assist in anchoring the basal keratinocyte to the underlying plasma membrane. Planes of division within the DEJ include the lamina lucida, lamina densa, and sublamina densa fibrillar region. (Courtesy of Randall Hayes.)

junctional EB-non-Herlitz, and has been described in a rare variant of EB simplex.^{67–71}

$\alpha 6 \beta 4$ integrin is a membrane glycoprotein component of the hemidesmosome, and defects in this integrin have been identified in a subset of patients with junctional EB in combination with pyloric atresia.^{72–75} Laminin-5 is a glycoprotein localized mainly to the lamina densa and lower lamina lucida,⁷⁶ and is also associated predominantly with hemidesmosomes.⁷⁷ Mutations in the genes encoding various chains of laminin-5 have been identified in patients with the lethal (Herlitz) junctional type of EB.^{78–81}

Type IV collagen predominates in the lamina densa region, whereas type VII collagen, which is also known as the epidermolysis bullosa acquisita (EBA) antigen, is situated in the zone beneath the lamina densa. EBA antigen was so named because it was first defined by circulating autoantibodies in the sera of patients with EBA, an acquired autoimmune blistering disease.⁸² The dystrophic forms of inherited EB have been shown to be a result of defects in the gene encoding type VII collagen.⁸³

Dermis and subcutaneous fat

The dermis of human skin consists primarily of connective tissues, including proteins (collagen and elastic tissue) and ground substance. This compartment lies between the epidermis superiorly and the subcutaneous fat inferiorly and forms a resilient and flexible layer that envelops the entire organism. It is divided into superficial (papillary) and deep (reticular) components, which are anatomically divided by a thin plexus of blood vessels. Although differentiation between these dermal compartments can be ascertained on the basis of the size of the collagen fiber bundles in adult skin, this criterion is less helpful in newborn skin, where there is a more gradual transition in fiber bundle size.² Structures found within the dermis, which are discussed in different sections of this chapter, include the cutaneous appendages (pilosebaceous units, eccrine and apocrine sweat glands), as well as nerves, blood vessels, and lymphatics.

Collagen is the major constituent of mammalian dermis and accounts for approximately 75% of the dry weight of the skin.¹⁹ The collagens are a family of related, yet individually distinct, structural proteins, and in the skin, they provide tensile strength and elasticity. Types I and III collagen are the major collagens found in human dermis, and smaller amounts of types IV (a primary component of the basement membrane as noted above), V, VI, and VII are also present.⁸⁴ Some 80–90% of dermal collagen is type I. Type III collagen was initially termed ‘fetal collagen’ because of its predominance in fetal tissues, where it accounts for over half of total skin collagen. However, synthesis of type I collagen accelerates during the postnatal period, and eventually, the ratio of type I to type III collagen increases, such that in adult skin it is around 5:1–6:1.⁸⁵ Abnormalities in collagen synthesis or post-translational processing may result in clinical disease, including osteogenesis imperfecta and the Ehlers–Danlos syndromes.

Elastic fibers play an important role in the structure and function of skin, providing elasticity and resilience. They consist of two components: elastin, which is a connective tissue protein, and elastic fiber-associated microfibrillar component, a complex of glycoproteins.⁸⁴ Elastic fibers are distributed in the papillary and reticular dermis. Fibers in the papillary dermis have been subdivided into elaunin fibers, which are oriented parallel to the DEJ, and oxytalan fibers, which connect the elaunin fibers to the DEJ.¹ It has been demonstrated that elastic fibers are distributed in the term newborn dermis in a manner similar to that of the adult, albeit with a decreased elastin content in the papillary dermal bundles, and with a finer fiber diameter in the reticular dermis.² The most widely recognized disease related to abnormalities in elastin production is cutis laxa, a heterogeneous group of disorders featuring lax skin and occasional systemic involvement in the form of hoarseness, emphysema, hernias, and diverticulae.⁸⁶

The ground substance of the dermis is an amorphous material that surrounds and embeds the fibrous and cellular components found in this compartment. Glycosaminoglycans (GAGs), which are long chains of aminated sugars, and proteoglycans (PGs), which are large molecules consisting of a core polypeptide linked to GAGs, are major constituents of ground substance.^{1,19} Major GAGs and PGs in the dermis are chondroitin sulfate, dermatan sulfate, heparin/heparin sulfate, chondroitin 6-sulfate, and hyaluronic acid (hyaluronan).^{1,19,87} These components are capable of retaining large amounts of water and may also play a role in binding growth factors and providing structural support, anticoagulation, and adhesion.^{1,88,89} Hyaluronic acid has been demonstrated in large amounts in fetal dermis and amniotic fluid and is thought by some to be associated with the rapid wound healing without scarring that has been observed to occur in fetal wounds.⁹⁰ These observations have been applied to the study of diabetic ulcers, where hyaluronic acid levels have been shown to be decreased, leading to the hypothesis that application of this substance may induce healing.⁹¹ Fibronectin is a large glycoprotein also found in the dermis and is associated with a variety of putative functions, including organization of the extracellular matrix, wound healing, attachment, and chemotaxis.^{1,19} More recent evidence suggests that dermal extracellular matrix components (fibronectin and chondroitin sulfate) and possibly the paucity of elastin compared with adult skin, as well as circulating amniotic stem cells, may play a role in fetal scarless healing.⁹²

The subcutaneous fat is an important layer, playing a role in shock absorption, energy storage, and maintenance of body

heat. The individual cells in the subcutaneous fat – adipocytes – form lobules that are separated by fibrous septa. The fibrous septa contain neural and vascular elements and connect deeper with the fascia of underlying skeletal muscle. In contrast, brown adipose tissue (BAT or brown fat) is a distinct type of adipose tissue, traditionally believed to be present only in newborns, that plays a vital role in neonatal thermoregulation (discussed in more detail later) through the oxidation of fatty acids.⁹³ BAT makes up 2–6% of the neonate’s total body weight and is found primarily in the scapular region, the mediastinum, around the kidneys and adrenal glands, and in the axilla.⁹⁴ The nonshivering thermogenesis that occurs in this tissue appears to be regulated by the enzyme-uncoupling protein thermogenin (more recently known as uncoupling protein 1 or UCP-1), which serves as a protonophore through the mitochondrial membrane, enabling high rates of cellular respiration and proton conductivity.⁹⁵ BAT is believed to be depleted over time, although recent studies suggest that functionally active BAT is present in at least some adults.⁹⁶

Pilosebaceous units, apocrine glands, and nails

HAIR FOLLICLES

The earliest hair follicles begin to form at 9–12 weeks’ gestation⁹⁷ primarily in a facial location, and the bulk of the remaining hairs start developing around 16–20 weeks, progressing in a cephalocaudal fashion.^{97,98} In some full-term infants, and especially in premature infants, the skin surface is covered with lanugo hairs, which are soft, fine hairs with limited growth potential.² These hairs are usually shed by term, or shortly thereafter, and are replaced by vellus hairs, which are eventually replaced on the scalp by coarse terminal hairs. The growth of a hair follicle is cyclic, the stages being divided into anagen (active growth), catagen (transitional involution), and telogen (resting) phases. The typical length of each of these phases is 2–5 years, 3 days, and 3 months, respectively.⁹⁸ No new hair follicles are formed after birth. The majority of hairs present at birth are synchronized in their growth phase.^{3,99} However, the initiation of hair production occurs in waves, such that follicles in the frontal and parietal regions of the neonate are already converting to the telogen phase, whereas occipital scalp hair progresses towards the telogen phase between 8 and 12 weeks’ postnatal age.¹⁰⁰ This contributes to the frequent appearance of temporary occipital alopecia in young infants. The hair follicle is organized into a series of concentric cellular compartments, the details of which are beyond the scope of this chapter. The structure of a pilosebaceous unit is depicted in [Figure 2.5](#). Longitudinally, the hair follicle can be divided into three zones: the infundibulum, extending from the opening of the follicle to the entrance of the sebaceous duct; the isthmus, extending from the entrance of the sebaceous duct to the insertion of the arrector pili muscle; and the inferior segment, which forms the remainder of the follicle from the insertion of the pili muscle to the base. A subpopulation of hair follicle keratinocytes has been identified in the upper follicle near the insertion site of the arrector pili.^{101,102} This area has been termed ‘the bulge’, and these cells may be involved not only in the regeneration of the anagen hair follicle, but also in the long-term maintenance of the epidermis.¹⁰³ Within the specialized environment of the bulge are multipotent stem cells, Merkel cells, and melanocytes, which are thought to interact, leading to the differentiation of

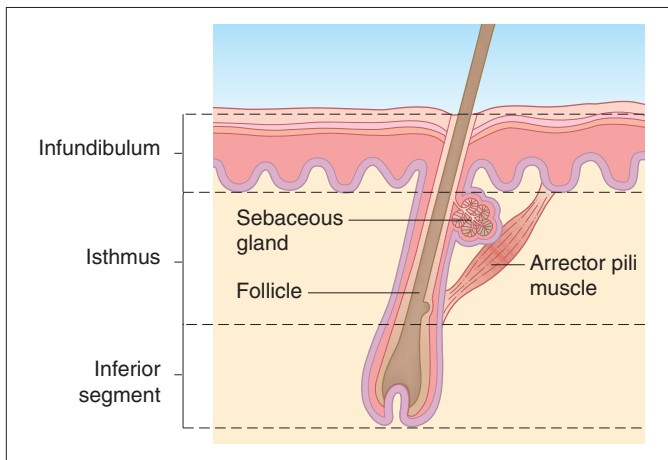


Figure 2.5 The pilosebaceous unit, divided into three zones: the infundibulum, extending from the opening of the follicle to the entrance of the sebaceous duct; the isthmus, extending from the entrance of the sebaceous duct to the insertion of the arrector pili muscle; and the inferior segment, extending from the insertion of the arrector pili muscle to the base. (Courtesy of Randall Hayes.)

stem cells into the components of the hair follicle, sebaceous gland and epidermis.^{104–107} The exact signaling and control of these stem cells is not known, but it appears that Lhx2 transcription factor plays an important role in their regulation in addition to adhesion molecules, epidermal growth factor, nerve growth factor, and platelet-derived growth factor.^{106,107} Lhx2 has been shown to have a role in regulation of these bulge region stem cells in embryonic and postnatal hair follicle growth and in wound healing.^{107–109} The integrity of the hair shaft is related to its protein constituents, including the intermediate filament hair keratins and high-sulfur proteins, and to the strong disulfide bonding between these proteins.⁹⁸ In neonates, hair may be a source of valuable clinical information: neonatal hair shaft analysis as a marker for intrauterine exposure to drugs of abuse having emerged as a useful tool over the last decade.^{103–115}

SEBACEOUS GLANDS

Sebaceous glands begin to develop between 13 and 15 weeks of fetal life.¹¹⁶ They are nearly always associated with hair follicles and are found diffusely in the skin, except on the palms, soles, and dorsal feet.¹¹⁷ The locations of the most prominent glands are the face and scalp, and in term neonates, may be quite evident over the nose, forehead, and cheeks. Modified glands are found in the skin of the nipples and areolae (Montgomery's tubercles), on the labia minora and prepuce (Tyson's glands), on the vermillion border of the lips (Fordyce's condition), and in the eyelids (meibomian glands). Sebaceous glands are well formed at birth and are quite active during the neonatal period, when they are stimulated by transplacentally derived steroid hormones and possibly by endogenous steroid production.³ This sebaceous activity in the newborn is reflected by the common finding of neonatal acne. Sebum, the substance produced by the holocrine sebaceous glands, is a composite of triglycerides, wax esters, squalene, cholesterol, and cholesterol esters and serves a role in lubrication of the follicle and epidermal surface.¹ Sebum levels sharply decline over the first year of life,¹¹⁸ putatively in response to diminished levels of circulating

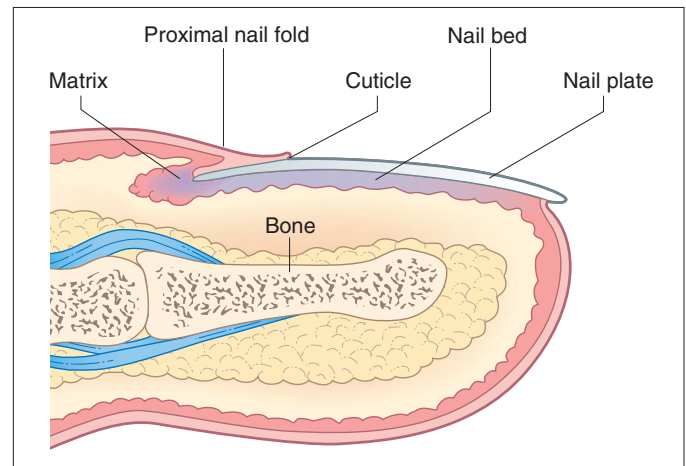


Figure 2.6 The nail unit. The hard nail plate consists of cornified cells and is produced by the mitotically active cells of the nail matrix, which is situated underneath the proximal nail fold. (Courtesy of Randall Hayes.)

hormones. The glands then remain relatively quiescent, producing only small amounts of sebum, until puberty.²

APOCRINE GLANDS

The apocrine glands are limited in distribution and are found primarily in the axillae, areolae, mons pubis, labia minora, scrotum, perianal area, external ear canal, and eyelids (Moll's glands).¹¹⁷ Their function in humans is unclear, although they may serve as scent glands. Apocrine glands remain small until puberty, when they enlarge and begin the process of secreting a milky white fluid. Body odor in postadolescent individuals is related to bacterial action on these secretions.

THE NAIL

The nail acts as a hard, protective covering over the distal end of the digit and may have served a function in evolution to assist in grasping small objects. The nail unit is depicted in Figure 2.6. The nail plate consists of cornified cells with a high protein content (primarily keratin) and is produced by the matrix, a cellular zone situated underneath the proximal nail fold at the base of the nail. The nail plate is situated on top of the nail bed, a highly vascular zone. The lateral nail folds consist of skin that envelops the lateral borders of the nail plate. The average growth rate of the human fingernail is 0.10–0.12 mm/day and appears to be greatest during the second decade of life.¹¹⁹ Toenails, which grow at a slower rate, may appear to be abnormal or 'ingrown' in newborns as a result of relative nail plate hypoplasia with a bulbous distal phalanx.¹²⁰ Despite their abnormal appearance, these nails eventually grow out and take on a more normal appearance.

Eccrine glands and neonatal sweating

Eccrine sweating is a physiologic response to increased body temperature and is the most effective means by which humans regulate their body temperature through evaporative heat loss.¹²¹ Gestational age, postnatal age, and body site are all important variables with regard to eccrine glands, and much of what is known about the process of neonatal sweating has been

learned from studies of the normal physiologic eccrine gland responses of term and preterm neonates to various sweat-inducing stimuli.

Eccrine sweat glands first appear during fetal development at 14 weeks and are initially limited to the volar surface of the hands and feet.¹²² They then appear in the axillae and eventually in a generalized distribution, with a full complement of anatomically normal glands present by the 28 weeks' gestation, although functionally, the glands are immature until 36 weeks' gestation.¹²³ The total number of eccrine sweat glands is formed before birth¹¹² and is estimated to be between 2 and 4 million.¹²²

The eccrine sweat gland consists of two segments: a secretory coil and a duct. The secretory coil is composed of secretory cells and myoepithelial cells, the latter being contractile cells with smooth muscle-like characteristics.¹²² The duct is composed of two cell layers, the basal and luminal ductal cells, which are involved in secretion and reabsorption of solutes. Components of eccrine sweat include water, sodium, chloride, potassium, urea, lactate, and ammonia.¹²² Although newly formed sweat is isotonic, reabsorption of water and solutes occurs in the duct, such that the expelled product is hypotonic. Evaporation of sweat from the surface of skin removes 0.58 calories of heat for each gram of water that evaporates.¹²⁴

Eccrine sweat glands are innervated anatomically by fibers of the sympathetic nervous system, although functionally, they are under cholinergic influence, and acetylcholine is the major neurotransmitter released from the periglandular nerve endings.¹²² Circulating catecholamines can also have a stimulatory effect on eccrine sweat production,¹²⁴ as can a variety of other peptides or neurotransmitters.

Sweating can be induced by pharmacologic stimulation and by emotional or thermal stress, and all mechanisms appear to be developed to some extent at birth in term infants. Levels of sweat production in response to the intradermal injection of pharmacologic agents have been demonstrated to bear a direct relation to gestational age,^{125–128} as well as to birthweight.¹²⁵ Thermal stress-induced sweating, although present in infants, appears to require a greater thermal stimulus in neonates than in adults, and this response also appears to be less developed in premature infants,^{128–132} but increases with postnatal age.¹³⁰ However, the thermal stimulus of sweating is an important contributor to increased insensible water loss in certain infants at risk, such as those treated with phototherapy for hyperbilirubinemia¹³³ and those under radiant warmers.^{134,135} The core temperature at which sweating begins in full-term newborns has been estimated at around 37.2°C.¹³⁶

'Emotional sweating' also appears to be well developed at birth in full-term but not premature neonates.¹²³ In one study, skin conductance after heel prick for routine blood testing rose sharply, and to a greater extent, in infants of more advanced gestational ages,¹³⁷ supporting the role of postconceptual age in maturation of the sweating response to emotional stress. Another study using auditory stimuli revealed that the sympathetic nervous system innervating the eccrine glands developed over the first 10 weeks of life.¹³⁸

The process of neonatal sweating, therefore, appears to develop early anatomically in fetal life and functionally at later stages, and the sweating response appears to be well developed at birth in term but not preterm infants. Hypotheses on the potential mechanisms for progressive postnatal maturity of the sweating response include anatomic development of the sweat

gland, functional development of the gland, or nervous system maturation.¹³⁰

Nerves, vascular networks, and thermoregulation

The cutaneous neural and vascular networks both develop early in the fetus, and their architecture becomes organized into adult patterns with increasing postnatal age.² Nerve networks in the skin contain both somatic sensory and sympathetic autonomic fibers and function as innervation for arrector pili muscles, cutaneous blood vessels, and sweat glands, as well as serving as receptors for touch, pain, temperature, itch, and mechanical stimuli. Large myelinated fibers, which are cutaneous branches of musculoskeletal nerves, innervate the skin in a pattern similar to that of vascular supply, whereas sensory nerves follow segmental dermatomes, which often show some overlap. Although cutaneous nerve fibers in the neonate are similar in structure and distribution to those in the adult, ultramicroscopic examination has revealed a higher percentage of unmyelinated fibers with bundling of axons, suggesting cytoarchitectural immaturity or incomplete growth.¹³⁹

Sensory cutaneous nerves may end freely or in encapsulated terminals. Free nerve endings in skin represent the most important of sensory receptors and include penicillate fibers found in a subepidermal location in hairy skin,¹⁴⁰ multiple types of free endings in digital (non-hairy) skin,¹⁴¹ and papillary nerve endings found at the orifice of hair follicles.¹⁹ Free nerve endings may also be associated with Merkel cells, neurosecretory cells of uncertain biologic significance that are of epithelial derivation and which become scarce in human skin after fetal development.^{2,142,143} Studies suggest that Merkel cells may actually be trophic for developing nerves and therefore play an inductive role in the development of the human cutaneous nerve plexus.¹⁴⁴ Specialized sensory receptors are present to varying degrees at birth, including Pacinian corpuscles, which are well developed and abundant in palm and sole skin, and Meissner's corpuscles, which are not fully formed and undergo continued morphologic changes with age.²

The vasculature of human dermis comprises two plexuses that parallel the skin surface: one in the lower dermis (deep plexus) and one just beneath the papillary dermis (superficial plexus).¹¹⁷ These two systems are connected by intercommunicating vessels, and vertical vessel arcades project superiorly from the superficial plexus toward the epidermis to form papillary loops (Fig. 2.7). This subpapillary plexus also gives rise to vessels that infuse the periadnexal structures.¹¹⁷ The cutaneous vascular system also contains arteriovenous shunts, or glomi, which are specialized anastomoses that assist in the regulation of skin blood flow and thermoregulatory shunting.^{3,129} The cutaneous capillary network is fairly disordered at birth and assumes a more orderly network pattern by the second week of life,¹⁴⁵ with continued development until around 3 months.¹⁴⁶

Vasomotor tone is under the control of a complex series of neurogenic, myogenic, and pharmacologic mechanisms,³ and the ability to control skin blood flow is now known to be well developed in neonates.¹⁴⁷ It was previously suggested that skin blood flow and total peripheral blood flow both correlate inversely (and decrease) with increasing birthweight, gestational maturity, and postnatal age, along with the development of increasing peripheral vascular resistance.¹⁴⁸ However, studies of capillary blood cell velocity (CBV) in full-term infants have

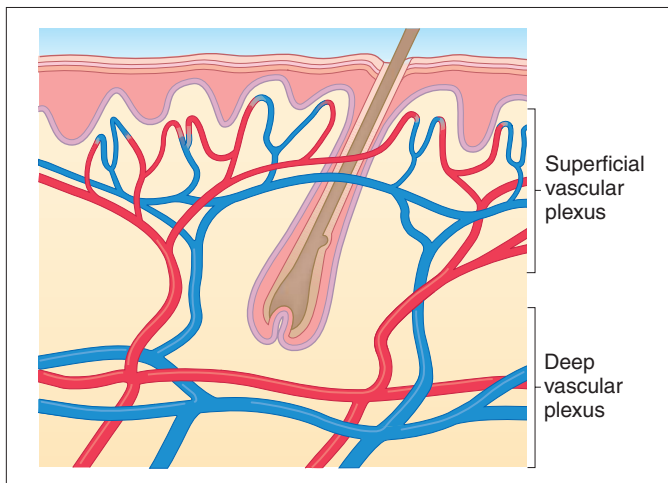


Figure 2.7 Vasculature of the skin, which is composed of the superficial plexus and the deep plexus with intercommunicating vessels. The superficial plexus gives rise to vertical vessel arcades that project superiorly into the dermal papillae and form papillary loops. (Courtesy of Randall Hayes.)

demonstrated a correlation between CBV and postnatal age, making the significance of previous microvascular findings in the neonate unclear.¹⁴⁹

Thermoregulation, which maintains an equilibrium between heat production and heat loss, is a crucial requirement in the neonate for maintenance of optimal core body temperature. It is a complex physiologic process under the control of the nervous (most importantly the hypothalamus) and endocrine systems. Although the thermoregulatory response is present in both term and preterm neonates, it is more pronounced in term infants.¹⁵⁰ The primary contributors to thermogenesis are muscles (voluntary and involuntary, or 'shivering' thermogenesis), sweat glands, blood vessels, and adipose tissue.¹⁵¹ Heat loss, or thermolysis, is accomplished by flow of heat from the center of the body to the surface and, subsequently, flow of heat from the body surface to the environment.¹⁵¹ Heat transfer to the surroundings can be accomplished through conduction (thermal exchange between the body surface and objects with which it is in contact), convection (heat loss from mass flow of moving air over the body surface), or radiation (electromagnetic heat loss to cool surfaces within the environment). Water evaporation, the fourth mechanism of heat loss, is discussed in the section on neonatal sweating, above.

Thermal stimuli providing information to the hypothalamus are transmitted from skin thermal receptors, as well as from deeper receptors present in the abdominal cavity and central nervous system.^{151,152} In general, increased environmental temperature results in cutaneous arteriolar vasodilatation and heat dissipation, whereas cold stress leads to vasoconstriction, with resultant decreased skin blood flow and reduced heat loss from the body core. Heat production in the neonate is accomplished primarily through nonshivering thermogenesis, which utilizes the increased number of mitochondria, increased glycogen stores, and abundant blood supply of brown adipose tissue.¹⁵² The primary mechanism utilized by the overheated neonate to dissipate heat is evaporative water loss through sweating.

Although temperature regulation is developed to some extent in most infants, they are susceptible to both cold and heat stress. Transition out of the stable thermal environment of

the uterus, as well as birth trauma, malformations, drugs, and respiratory deficiency, may predispose the newborn to hypothermia, whereas birth trauma and exogenous sources of heat may lead to hyperthermia.¹⁵¹ Studies of both full-term and preterm infants reveal a decreased ability to vasoconstrict blood vessels in the extremities following exposure to cool temperatures, further predisposing infants to hypothermia.^{136,153} Extremely low birthweight infants (400–1000 grams, with a corresponding gestational age of around 23–28 weeks) were shown to largely lack the ability to peripherally vasoconstrict in the face of hypothermia during the first 12 h of life. This finding likely reflects immature autoregulation, and may extrapolate to cerebral blood flow and explain the increased susceptibility of this population to brain injury.¹⁵⁴ Thermoregulation is a multifaceted process, which at times may be inadequate in the maintenance of the homeothermic state in the neonate. An understanding of these processes is therefore vital for providing appropriate thermal support to such infants.

Melanocytes and pigmentation of the skin

As mentioned, interspersed among the basal layer cells are the dendritic, melanin-producing cells called melanocytes. These cells first appear between a gestational age of 40 and 50 days and migrate to the skin from the neural crest.¹⁵⁵ Whereas melanocytes are found in both basal and suprabasal locations during embryogenesis, neonatal skin reveals a more limited distribution restricted to the basal epidermal layer.^{156,157} Melanin is manufactured within organelles called melanosomes, which are formed in melanocytes and transferred to neighboring keratinocytes via dendritic connections. Each melanocyte is in contact with roughly 36 keratinocytes, an association that is referred to as the epidermal melanin unit. The transfer of melanin from the melanocyte to the keratinocytes within this unit results in pigment being distributed in the basal layer, as well as more superficially, where melanin serves a protective role by absorbing and scattering ultraviolet radiation (UVR).¹⁹

Two forms of melanin are present in human skin: eumelanin, which is brown, and pheomelanins, which are red and yellow.^{130,158} Differences in native skin pigmentation among individuals are related to the concentration, as well as the distribution and retention, of melanin in the basal cell layer, rather than to the absolute number of melanocytes.^{1,159,160} Although melanocytes in newborn skin are quantitatively comparable with those in older individuals, melanin production, and hence skin pigmentation, is relatively decreased during the neonatal period,^{2,3} with gradual darkening over several months following birth. Several disorders of either increased or decreased pigmentation, as well as proliferation of melanocytes, are seen in the newborn period. These include disorders such as albinism, piebaldism, café-au-lait macules, congenital nevi, and others. Disorders of pigmentation and melanocytes are discussed in Chapters 23 and 24.

Cutaneous immunosurveillance, Langerhans' cells, and cytokines

CUTANEOUS IMMUNOSURVEILLANCE

While participating in the important roles of physical protection, barrier function, and thermoregulation, the skin also

occupies a niche in the immunologic system of the host as a peripheral immune organ. Various models and terms have been used to describe the immunologic capacities of the skin, including skin-associated lymphoid tissues (SALT), skin immune system (SIS), dermal microvascular unit (DMU), and dermal immune system (DIS).^{161,162} SALT are composed of epidermal Langerhans' cells and keratinocytes, as well as dermal endothelial cells and the skin-draining lymph nodes, and are an important system in the induction of immunity and tolerance.¹⁶² The broader terminology of the SIS refers to the entire complex interplay of immune response-related systems in the skin, including cellular components and humoral factors,^{162,163} and both dermal and epidermal components.

These immunologic systems in the skin provide cutaneous immunosurveillance, which functions in the prevention of the development of cutaneous neoplasms and mediates against persistent infections with intracellular pathogens.¹⁶⁴ Cellular components include keratinocytes, antigen-presenting cells (APCs), monocytes and macrophages, granulocytes, mast cells, lymphocytes, and endothelial cells, whereas humoral constituents include antimicrobial peptides, complement proteins, immunoglobulins, cytokines, and prostaglandins.¹⁶² Antimicrobial peptides and proteins are an important innate cutaneous defense mechanism against microbial intruders. They have a broad-spectrum killing activity, and their presence in both amniotic fluid and vernix caseosa has been well documented, suggesting that effective innate immune protection begins during fetal and early neonatal life.^{4,6,165,166} Human antimicrobial peptides include the cathelicidin, dermicidin and β -defensin families. Regulation of these peptides may involve Ca^{2+} , $1, 25(\text{OH})_2\text{VD}_3$, retinoic acids, and kallikreins.^{167,168}

Characterization of lymphocyte populations within normal human skin has revealed that they are predominantly T cells, with 90% of cells clustered around postcapillary venules or adjacent to cutaneous appendages.^{163,169} Intraepidermal localization of T lymphocytes accounts for less than 2% of skin lymphocytes normally present. B lymphocytes are not present in normal human skin, but may be found in mucosal locations.

LANGERHANS' CELLS

The cell that sets the SIS apart from others is the Langerhans' cell (LC). This APC resides in the epidermis and is involved in skin allograft rejection, delayed hypersensitivity reactions, and specific T-cell responses.¹⁷⁰ LCs are derived from the bone marrow and migrate via a hematogenous route to the skin. They are present in the fetus as early as 16 weeks' gestation, with early restriction to the basal layer and eventual distribution among suprabasal cells.¹⁷¹

The function of the LC was unclear until the 1970s, when surface Fc receptors, major histocompatibility complex (MHC) class II molecules, and C3 receptors were described on its surface,¹⁶⁴ suggesting an immunologic role. It is now well accepted that the epidermal LC is involved in antigen processing and presentation in a variety of skin-induced immune responses against a variety of antigens, including contact allergens, allo-antigens, tumor antigens, and microorganisms.¹⁷² These cells have been found to have positive staining for other characteristic surface markers, including CD1a and S100 proteins and membrane-bound adenosine triphosphatase (ATPase).¹⁷² Although the exact function of the CD1a glycoprotein remains

unclear, relatively weak expression of the antigen on LCs from neonatal skin has been demonstrated¹⁷³ and may partially explain why neonatal donor skin demonstrates extended survival compared to adult donor skin after transplantation in animal models.^{174–176} Ultrastructurally, LCs are found to contain Birbeck granules, distinctive cytoplasmic organelles with central striations and a characteristic 'tennis racket' appearance on thin electron micrograph sections.¹⁷⁰ Although the exact function of these granules is unknown, it has been suggested that they may be involved in receptor–ligand interactions and surface antigen trafficking.¹⁷⁷

LCs are a member of the dendritic family of cells, which are stellate cells with cytoplasmic extensions, or dendrites. Other dendritic APCs are present in human skin, including dermal dendritic cells, which also contribute to the surveillance function of the immune system and initiation of the primary immune response. These cells were also shown to express high levels of MHC class II molecules, as well as factor XIIIa, and are isolated primarily from the dermis.¹⁷⁸ Some dermal dendritic cells may acquire the ultrastructural characteristics of LCs and have been described to express Langerin (CD207), a C-type lectin receptor found on the surface of LCs and a major constituent of Birbeck granules.^{178,179} There are also Langerin-negative dermal dendritic cells. It appears that these different subtypes of dendritic cells may have independent and specific roles in presenting foreign substances and pathogens to the immune system.¹⁸⁰ In neonatal murine skin, LCs are less effective at antigen presentation, corresponding to less T-cell activation and the promotion of immune tolerance.¹⁸¹

CYTOKINES

In addition to the role of such cellular components in cutaneous immunity, a complex interplay with several humoral factors is also present, including the biologic proteins known as cytokines. These autocrine, paracrine, endocrine, exocrine, and intracrine proteins include the interleukins (ILs), interferons (IFNs), colony-stimulating factors (CSFs), tumor necrosis factors (TNFs), and growth factors (GFs).^{163,172} They are produced by various cell types, including keratinocytes, which have been demonstrated to be capable of secreting several types of cytokines.¹⁶³

Cytokines have multiple biologic functions and act on target cells by binding to specific receptors. The result of such binding is signal transduction to the cell interior followed by activation of various second-messenger pathways and eventual altered gene expression and cell function.¹⁷² For instance, on exposure to contact allergens, LCs may show enhanced migration after induction of local IL-1 β production, ultimately resulting in activation and expansion of allergen-specific T-cell populations,¹⁶² whereas IL-10 inhibits the ability of LCs to stimulate T cells.¹⁷⁰ Cytokines are involved in many cutaneous processes, both physiologic and pathologic, the details of which are beyond the scope of this chapter. Although not clearly elucidated, the secretion, activity, and effector functions of cytokines in neonates may differ from those in adults. In a study of immunity biomarkers, neonates ≤ 32 weeks' EGA had significantly greater levels of proinflammatory cytokines (including IL-1 β , IL-6 and IL-8) than full-term infants and adults.¹⁸² Another example is the newborn hypothalamic response to IL-1, also known as endogenous pyrogen. The synthesis of prostaglandins in response to this protein normally shifts the thermoregulatory

set-point, resulting in fever, but this responsiveness is decreased in the neonate, which may account for the attenuated fever response in the setting of infection.¹⁵⁸ Abnormalities in the control of proinflammatory cytokines may lead to a variety of clinical disorders, often grouped under the 'cryopyrin-associated periodic syndromes'. Deficiency of the interleukin 1-receptor antagonist (DIRA) is one such condition, which presents as fetal

distress, a severe pustular exanthem, joint swelling, bone lesions and pain in neonates, and has been successfully treated with anakinra, a recombinant human IL-1 receptor antagonist which blocks the effects of IL-1 β .¹⁸³

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KEY REFERENCES

12. Evans NJ, Rutter N. Development of the epidermis in the newborn. *Biol Neonate* 1986;49: 74–80.
23. Odland GF, Holbrook K. The lamellar granules of epidermis. *Curr Probl Dermatol* 1981;9: 29–49.
26. Elias PM. Epidermal lipids, barrier function and desquamation. *J Invest Dermatol* 1983; 80(Suppl):44S–9S.
39. Hammarlund K, Sedin G, Stromberg B. Trans-epidermal water loss in newborn infants. VIII. Relation to gestational age and post-natal age in appropriate and small for gestational age infants. *Acta Paediatr Scand* 1983;72:721–8.
41. Harpin VA, Rutter N. Barrier properties of the newborn infant's skin. *J Pediatr* 1983;102: 419–24.
46. Hanley K, Jiang Y, Elias PM, et al. Acceleration of barrier ontogenesis in vitro through air exposure. *Pediatr Res* 1997;41:293–9.
48. Fluhr JW, Darlenski R, Lachmann N, et al. Infant epidermal skin physiology: adaptation after birth. *Br J Dermatol* 2012;166: 483–90.
76. Stanley JR, Woodley DT, Katz SI, et al. Structure and function of basement membrane. *J Invest Dermatol* 1982;79:69S–72S.
156. Haake AR, Scott GA. Physiologic distribution and differentiation of melanocytes in human fetal and neonatal skin equivalents. *J Invest Dermatol* 1991;96:71–7.
163. Bos JD, Kapsenberg ML. The skin immune system: progress in cutaneous biology. *Immunol Today* 1993;14:75–8.

REFERENCES

- White CR, Bigby M, Sanguenza OP. What is normal skin? In: Arndt KA, LeBoit PE, Robinson JK, et al, editors. *Cutaneous medicine and surgery. An integrated program in dermatology*. Philadelphia: WB Saunders; 1996. p. 3–45.
- Holbrook KA. A histological comparison of infant and adult skin. In: Maibach HI, Boissits EK, editors. *Neonatal skin, structure and function*. New York: Marcel Dekker; 1982. p. 3–31.
- Solomon LM, Esterly NB. Neonatal dermatology. I. The newborn skin. *J Pediatr* 1970;77: 888–94.
- Marchini G, Lindow S, Brismar H, et al. The newborn infant is protected by an innate antimicrobial barrier: peptide antibiotics are present in the skin and vernix caseosa. *Br J Dermatol* 2002;147:1127–34.
- Visscher MO, Narendran V, Pickens WL, et al. Vernix caseosa in neonatal adaptation. *J Perinatol* 2005;25:440–6.
- Yoshio H, Tollin M, Gudmundsson GH, et al. Antimicrobial polypeptides of human vernix caseosa and amniotic fluid: implications for newborn innate defense. *Pediatr Res* 2003;53: 211–6.
- Yoshio H, Lagercrantz H, Gudmundsson GH, et al. First line of defense in early human life. *Semin Perinatol* 2004;28:304–11.
- Visscher MO, Utturkar R, Pickens WL, et al. Neonatal skin maturation – Vernix caseosa and free amino acids. *Pediatr Dermatol* 2011; 28(2):122–32.
- Visscher MO, Barai N, LaRuffa AA, et al. Epidermal barrier treatments based on vernix caseosa. *Skin Pharmacol Physiol* 2011;24(6): 322–9.
- Serri F, Montagna W. The structure and function of the epidermis. *Pediatr Clin North Am* 1961;8:917–41.
- Holbrook KA, Sybert VP. Basic science. In: Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 2nd ed. New York: Churchill Livingstone; 1995. p. 1–70.
- Evans NJ, Rutter N. Development of the epidermis in the newborn. *Biol Neonate* 1986;49:74–80.
- Wickett RR, Mutschelknaus JL, Hoath SB. Ontogeny of water sorption-desorption in the perinatal rat. *J Invest Dermatol* 1993;100: 407–11.
- Fuchs E. Keratins: mechanical integrators in the epidermis and hair and their role in disease. *Prog Dermatol* 1996;30:1–12.
- Fuchs E, Weber K. Intermediate filaments: structure, dynamics, function, and disease. *Annu Rev Biochem* 1994;63:345–82.
- Byrne C, Tainsky M, Fuchs E. Programming gene expression in developing epidermis. *Development* 1994;120:2369–83.
- Coolen NA, Schouten KC, Middelkoop E, et al. Comparison between human fetal and adult skin. *Arch Dermatol Res* 2010;302:47–55.
- Bressler RS, Bressler CH. Functional anatomy of the skin. *Clin Podiatr Med Surg* 1989;6: 229–46.
- Haake AR, Holbrook KA. The structure and development of skin. In: Freedberg IM, Eisen AZ, Wolff K, et al., editors. *Dermatology in general medicine*. 5th ed. New York: McGraw-Hill; 1999. p. 70–114.
- Dale BA, Holbrook KA, Steinert PM. Assembly of stratum corneum basic protein and keratin filaments in macrofibrils. *Nature* 1978;276: 729–31.
- Manabe M, Sanchez M, Sun TT, et al. Interaction of filaggrin with keratin filaments during advanced stages of normal human epidermal differentiation and in ichthyosis vulgaris. *Differentiation* 1991;48:43–50.
- Kezic S, Kammeyer A, Calkoen F, et al. Natural moisturizing factor components in the stratum corneum as biomarkers of filaggrin genotype: evaluation of minimally invasive methods. *Br J Dermatol* 2009;161:1098–104.
- Odland GF, Holbrook K. The lamellar granules of epidermis. *Curr Probl Dermatol* 1981;9: 29–49.
- Akiyama M, Sugiyama-Nakagiri Y, Sakai K, et al. Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. *J Clin Invest* 2005; 115(7):1777–84.
- Elias PM. Lipids and the epidermal permeability barrier. *Arch Dermatol Res* 1981;270: 95–117.
- Elias PM. Epidermal lipids, barrier function and desquamation. *J Invest Dermatol* 1983;80(Suppl):44S–9S.
- Proksch E, Holleran WM, Menon GK, et al. Barrier function regulates epidermal lipid and DNA synthesis. *Br J Dermatol* 1993;128: 473–82.
- Elias PM, Feingold KR. Lipids and the epidermal water barrier: metabolism, regulation, and pathophysiology. *Semin Dermatol* 1992;11: 176–82.
- Grubauer G, Feingold KR, Harris RM, et al. Lipid content and lipid type as determinants of the epidermal permeability barrier. *J Lipid Res* 1989;30:89–96.
- Elias PM. Dynamics of the epidermal barrier: New implications for percutaneous drug delivery, topical therapeutics and disease pathogenesis. *Prog Dermatol* 1992;26:1–8.
- Friberg SE. Micelles, microemulsions, liquid crystals, and the structure of stratum corneum lipids. *J Soc Cosmet Chem* 1990;41:155–71.
- Elias PM, Goerke J, Friend DS. Mammalian epidermal barrier layer lipids: Composition and influence on structure. *J Invest Dermatol* 1977;69:535–46.
- Elias PM, Friend DS. The permeability barrier in mammalian epidermis. *J Cell Biol* 1975;65: 180–91.
- Aszterbaum M, Menon GK, Feingold KR, et al. Ontogeny of the epidermal barrier to water loss in the rat: Correlation of function with stratum corneum structure and lipid content. *Pediatr Res* 1992;31:308–17.
- Menon GK, Feingold KR, Moser AH, et al. De novo sterogenesis in the skin. II. Regulation by cutaneous barrier requirements. *J Lipid Res* 1985;26:418–27.
- Grubauer G, Feingold KR, Elias PM. Relationship of epidermal lipogenesis to cutaneous barrier function. *J Lipid Res* 1987;28: 746–52.
- Monger DJ, Williams ML, Feingold KR, et al. Localization of sites of lipid biosynthesis in mammalian epidermis. *J Lipid Res* 1988;29: 603–11.
- Williams ML, Aszterbaum M, Menon GK, et al. Preservation of permeability barrier ontogenesis in the intrauterine growth-retarded fetal rat. *Pediatr Res* 1993;33:418–24.
- Hammarlund K, Sedin G, Stromberg B. Transepidermal water loss in newborn infants. VIII. Relation to gestational age and post-natal age in appropriate and small for gestational age infants. *Acta Paediatr Scand* 1983;72:721–8.
- Barker N, Hadgraft J, Phil D, et al. Skin permeability in the newborn. *J Invest Dermatol* 1987;88:409–11.
- Harpin VA, Rutter N. Barrier properties of the newborn infant's skin. *J Pediatr* 1983;102: 419–24.
- Evans NJ, Rutter N. Percutaneous respiration in the newborn infant. *J Pediatr* 1986;108: 282–6.
- Rutter N. The immature skin. *Br Med Bull* 1988;44:957–70.
- Hammarlund K, Sedin G. Transepidermal water loss in newborn infants. III. Relation to gestational age. *Acta Paediatr Scand* 1979;68: 795–801.
- Kalia YN, Nonato LB, Lund CH, et al. Development of skin barrier function in premature infants. *J Invest Dermatol* 1998;111:320–6.
- Hanley K, Jiang Y, Elias PM, et al. Acceleration of barrier ontogenesis in vitro through air exposure. *Pediatr Res* 1997;41:293–9.
- Jiang YJ, Barish G, Lu B, et al. PPAR δ activation promotes stratum corneum formation and epidermal barrier development during late gestation. *J Invest Dermatol* 2010;130: 511–19.
- Fluhr JW, Darlenski R, Lachmann N, et al. Infant epidermal skin physiology: adaptation after birth. *Br J Dermatol* 2012;166:483–90.
- Nikolovski J, Stamatas GN, Kollias N, et al. Barrier function and water holding and transport properties of infant stratum corneum are different from adult and continue to develop through the first year of life. *J Invest Dermatol* 2008;128:1728–36.
- Bustamante SA, Steslow J. Use of a transparent adhesive dressing in very low birthweight infants. *J Perinatol* 1989;9:165–9.
- Knauth AK, Gordin M, McNelis W, et al. Semi-permeable polyurethane membrane as an artificial skin for the premature neonate. *Pediatrics* 1989;83:945–50.
- Vernon HJ, Lane AT, Wischerath LJ, et al. Semi-permeable dressing and transepidermal water loss in premature infants. *Pediatrics* 1990;86: 835–47.
- Mancini AJ, Sookdeo-Drost S, Madison KC, et al. Semipermeable dressings improve epidermal barrier function in premature infants. *Pediatr Res* 1994;36:306–14.
- Lane AT, Drost SS. Effects of repeated application of emollient cream to premature neonates' skin. *Pediatrics* 1993;92:415–9.
- Nopper AJ, Horii KA, Sookdeo-Drost S, et al. Topical ointment therapy benefits premature infants. *J Pediatr* 1996;128:660–9.
- Fluhr JW, Darlenski R, Taieb A, et al. Functional skin adaptation in infancy – almost complete but not fully competent. *Exp Dermatol* 2010;19:483–92.
- Corsini E, Sangha N, Feldman SR. Epidermal stratification reduces the effects of UVB (but not UVA) on keratinocyte cytokine production and cytotoxicity. *Photodermatol Photoimmunol Photomed* 1997;13:147–52.
- Jackson SM, Elias PM. Skin as an organ of protection. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al, editors. *Dermatology in general*

- medicine. 4th ed. New York: McGraw-Hill; 1993. p. 241–53.
59. Wyatt JE, Poston SM, Noble WC. Adherence of *Staphylococcus aureus* to cell monolayers. *J Appl Bacteriol* 1990;69:834–44.
 60. Romero-Steiner S, Witek T, Balish E. Adherence of skin bacteria to human epithelial cells. *J Clin Microbiol* 1990;28:27–31.
 61. Darmstadt GL, Fleckman P, Jonas M, et al. Differentiation of cultured keratinocytes promotes the adherence of *Streptococcus pyogenes*. *J Clin Invest* 1998;101:128–36.
 62. Ebling FJ. Functions of the skin. In: Champion RH, Burton JL, Ebling FJG, editors. *Textbook of dermatology*. 5th ed. Oxford: Blackwell Scientific; 1992. p. 125–55.
 63. Hurley HJ. Permeability of the skin. In: Moschella SL, Hurley HJ, editors. *Dermatology*. 3rd ed. Philadelphia: WB Saunders; 1992. p. 101–6.
 64. Woodley D, Sauder D, Talley MJ, et al. Localization of basement membrane components after dermal–epidermal junction separation. *J Invest Dermatol* 1983;81:149–53.
 65. Pulkkinen L, Uitto J. Hemidesmosomal variants of epidermolysis bullosa. Mutations in the Greek $\alpha 6\beta 4$ integrin and the 180-kDa bullous pemphigoid antigen/type XVII collagen genes. *Exp Dermatol* 1998;7:46–64.
 66. Zone JJ, Taylor TB, Meyer LJ, et al. The 97 kDa linear IgA bullous disease antigen is identical to a portion of the extracellular domain of the 180 kDa bullous pemphigoid antigen, BPAG2. *J Invest Dermatol* 1998;110:207–10.
 67. Powell AM, Sakuma-Oyama N, Oyama N, et al. Collagen XVII/BP180: a collagenous transmembrane protein and component of the dermoepidermal anchoring complex. *Clin Exp Dermatol* 2005;30:682–7.
 68. Jonkman MF, deJong MC, Heeres K, et al. 180-kD bullous pemphigoid antigen (BP180) is deficient in generalized atrophic benign epidermolysis bullosa. *J Clin Invest* 1995;95:1345–52.
 69. Pohla-Gubo G, Lazarova Z, Giudice GJ, et al. Diminished expression of the extracellular domain of bullous pemphigoid antigen 2 (BPAG2) in the epidermal basement membrane of patients with generalized atrophic benign epidermolysis bullosa. *Exp Dermatol* 1995;4:199–206.
 70. Gatalica B, Pulkkinen L, Li K, et al. Cloning of the human type XVII collagen gene (COL17A1), and detection of novel mutations in generalized atrophic benign epidermolysis bullosa. *Am J Hum Genet* 1997;60:352–65.
 71. Huber M, Floeth M, Borradori L, et al. Deletion of the cytoplasmic domain of BP180/collagen XVII causes a phenotype with predominant features of epidermolysis bullosa simplex. *J Invest Dermatol* 2002;118:185–92.
 72. Vidal F, Aberdam D, Miquel C, et al. Integrin beta 4 mutations associated with junctional epidermolysis bullosa with pyloric atresia. *Nature Genet* 1995;10:229–34.
 73. Pulkkinen L, Bruckner-Tuderman L, et al. Compound heterozygosity for missense (L156P) and nonsense (R554X) mutations in the beta4 integrin gene (ITGB4) underlies mild, nonlethal phenotype of epidermolysis bullosa with pyloric atresia. *Am J Pathol* 1998;152:935–41.
 74. Ruzzi L, Gagnoux-Palacios L, Pinola M, et al. A homozygous mutation in the integrin alpha6 gene in junctional epidermolysis bullosa with pyloric atresia. *J Clin Invest* 1997;99:2826–31.
 75. Brown TA, Gil SG, Sybert VP, et al. Defective integrin alpha 6 beta 4 expression in the skin of patients with junctional epidermolysis bullosa and pyloric atresia. *J Invest Dermatol* 1996;107:384–91.
 76. Stanley JR, Woodley DT, Katz SI, et al. Structure and function of basement membrane. *J Invest Dermatol* 1982;79:69S–72S.
 77. Masunaga T, Shimizu H, Ishiko A, et al. Localization of laminin-5 in the epidermal basement membrane. *J Histochem Cytochem* 1996;44:1223–30.
 78. Uitto J, Pulkkinen L, Christiano AM. Molecular basis of the dystrophic and junctional forms of epidermolysis bullosa: mutations in the type VII collagen and kalinin (laminin 5) genes. *J Invest Dermatol* 1994;103:39S–46S.
 79. Pulkkinen L, McGrath J, Airenne T, et al. Detection of novel LAMC2 mutations in Herlitz junctional epidermolysis bullosa. *Mol Med* 1997;3:124–35.
 80. Kivirikko S, McGrath JA, Pulkkinen L, et al. Mutational hotspots in the LAMB3 gene in the lethal (Herlitz) type of junctional epidermolysis bullosa. *Hum Mol Genet* 1996;5:231–7.
 81. Kivirikko S, McGrath JA, Baudoin C, et al. A homozygous nonsense mutation in the alpha 3 chain gene of laminin 5 (LAMA3) in lethal (Herlitz) junctional epidermolysis bullosa. *Hum Mol Genet* 1995;4:959–62.
 82. Woodley DR. Importance of the dermal–epidermal junction and recent advances. *Dermatologica* 1987;174:1–10.
 83. Hovnanian A, Rochat A, Bodemer C, et al. Characterization of 18 new mutations in COL7A1 in recessive dystrophic epidermolysis bullosa provides evidence for distinct molecular mechanisms underlying defective anchoring fibril formation. *Am J Hum Genet* 1997;61:599–610.
 84. Uitto J, Olsen DR, Fazio MJ. Extracellular matrix of the skin: 50 years of progress. *J Invest Dermatol* 1989;92:61S–77S.
 85. Uitto J, Perejda AJ, Abergel RP, et al. Altered steady-state ratio of type I/III procollagen mRNAs correlates with selectively increased type I procollagen biosynthesis in cultured keloid fibroblasts. *Proc Natl Acad Sci USA* 1985;82:5935–9.
 86. Micali G, Bene-Bain MA, Guitart J, et al. Genodermatoses. In: Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 2nd ed. New York: Churchill Livingstone; 1995. p. 347–411.
 87. Couchman JR, Caterson B, Christner JE, et al. Mapping by monoclonal antibody detection of glycosaminoglycans in connective tissues. *Nature* 1984;307:650–2.
 88. Hardingham TE, Fosang AJ. Proteoglycans: many forms and many functions. *FASEB J* 1992;6:861–70.
 89. Scott JE. Proteoglycan: collagen interactions and subfibrillar structure in collagen fibrils. Implications in the development and ageing of connective tissues. *J Anat* 1990;169:23–35.
 90. Longaker MT, Adzick NS, Hall JL, et al. Studies in fetal wound healing. VII. Fetal wound healing may be modulated by hyaluronic acid stimulating activity in amniotic fluid. *J Pediatr Surg* 1990;25:430–3.
 91. Colwell AS, Longaker MT, Lorenz HP. Fetal wound healing. *Front Biosci* 2003;8:s1240–8.
 92. Klein JD, Turner CG, Steigman SA, et al. Amniotic mesenchymal stem cells enhance normal fetal wound healing. *Stem Cells Dev* 2011;20:969–76.
 93. West DP, Worobec S, Solomon LM. Pharmacology and toxicology of infant skin. *J Invest Dermatol* 1981;76:147–50.
 94. Buczkowski-Bickmann MK. Thermoregulation in the neonate and the consequences of hypothermia. *Clin Forum Nurse Anesth* 1992;3:77–82.
 95. Nedergaard J, Cannon B. Brown adipose tissue: development and function. In: Polin RA, Fox WW, editors. *Fetal and neonatal physiology*. 2nd ed. Philadelphia: WB Saunders; 1998. p. 478–89.
 96. Tews D, Wabitsch M. Renaissance of brown adipose tissue. *Horm Res Pediatr* 2011;75:231–9.
 97. Muller M, Jasmin JR, Monteil RA, et al. Embryology of the hair follicle. *Early Hum Dev* 1991;26:159–66.
 98. Bertolino AP, Klein LM, Freedberg IM. Biology of hair follicles. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al., editors. *Dermatology in general medicine*. 4th ed. New York: McGraw-Hill; 1993. p. 289–93.
 99. Barman JM, Pecoraro V, Astore I, et al. The first stage in the natural history of the human scalp hair cycle. *J Invest Dermatol* 1967;48:138–42.
 100. Gareri J, Koren G. Prenatal hair development: Implications for drug exposure determination. *Forensic Sci Int* 2010;196:27–31.
 101. Cotsarelis G, Sun TT, Lavker RM. Label-retaining cells reside in the bulge area of pilosebaceous unit: implications for follicular stem cells, hair cycle and skin carcinogenesis. *Cell* 1990;61:1329–37.
 102. Sun TT, Cotsarelis G, Lavker RM. Hair follicular stem cells: The bulge-activation hypothesis. *J Invest Dermatol* 1991;96:77S–8S.
 103. Yang JS, Lavker RM, Sun TT. Upper human hair follicle contains a subpopulation of keratinocytes with superior in vitro proliferative potential. *J Invest Dermatol* 1993;101:652–9.
 104. Blanpain C, Lowry WE, Geoghegan A, et al. Self-renewal, multipotency, and the existence of two cell populations within an epithelial stem cell niche. *Cell* 2004;118:530–2.
 105. Christiano AM. Epithelial stem cells: stepping out of their niche. *Cell* 2004;118:530–2.
 106. Lavker RM, Sun TT, Oshima H, et al. Hair follicle stem cells. *J Invest Dermatol Symp Proc* 2003;8:28–38.
 107. Rhee H, Polak L, Fuch E. Lhx2 maintains stem cell character in hair follicles. *Science* 2006;312:1946–9.
 108. Tornqvist G, Sandberg A, Hagglund AC, et al. Cyclic expression of lhx2 regulates hair formation. *PLoS Genet* 2010;6(4):e1000904.
 109. Mardaryev AN, Meier N, Poterlowicz K, et al. Lhx2 differentially regulates Sox9, Tcf4, and Lgr5 in hair follicle stem cells to promote epidermal regeneration after injury. *Development* 2011;138:4843–52.
 110. Narisawa Y, Hashimoto K, Kohda H. Merkel cells participate in the induction and alignment of epidermal ends of arrector pili muscles of human fetal skin. *Br J Dermatol* 1996;134:494–8.
 111. Kim DK, Holbrook KA. The appearance, density, and distribution of Merkel cells in human embryonic and fetal skin: their relation to sweat gland and hair follicle development. *J Invest Dermatol* 1995;104:411–6.

112. Klein J, Forman R, Eliopoulos C, et al. A method for simultaneous measurement of cocaine and nicotine in neonatal hair. *Ther Drug Monit* 1994;16:67–70.
113. Koren G. Measurement of drugs in neonatal hair: a window to fetal exposure. *Forensic Sci Int* 1995;70:77–82.
114. Kintz P, Mangin P. Determination of gestational opiate, nicotine, benzodiazepine, cocaine and amphetamine exposure by hair analysis. *J Forensic Sci Soc* 1993;33:139–42.
115. Eliopoulos C, Klein J, Chitayat D, et al. Nicotine and cotinine in maternal and neonatal hair as markers of gestational smoking. *Clin Invest Med* 1996;19:231–42.
116. Pochi PE, Strauss JS, Downing DT. Age-related changes in sebaceous gland activity. *J Invest Dermatol* 1979;73:108–11.
117. Stal S, Spira M, Hamilton S. Skin morphology and function. *Clin Plast Surg* 1987;14:201–8.
118. Agache P, Blanc D, Barrant C, et al. Sebum levels during the first year of life. *Br J Dermatol* 1980;103:643–9.
119. Baden HP, Kvedar JC. Biology of nails. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al, editors. *Dermatology in general medicine*. 4th ed. New York: McGraw-Hill; 1993. p. 294–7.
120. Wagner AM, Hansen RC. Neonatal skin and skin disorders. In: Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 2nd ed. New York: Churchill Livingstone; 1995. p. 263–346.
121. Mancini AJ, Lane AT. Sweating in the neonate. In: Polin RA, Fox WW, editors. *Fetal and neonatal physiology*. 2nd ed. Philadelphia: WB Saunders; 1998. p. 767–70.
122. Sato K. Biology of the eccrine sweat gland. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al, editors. *Dermatology in general medicine*. 4th ed. New York: McGraw-Hill; 1993. p. 221–31.
123. Atherton DJ. The neonate. In: Champion RH, Burton JL, Ebling FJG, editors. *Textbook of dermatology*. 5th ed. Oxford: Blackwell Scientific; 1992. p. 382–3.
124. Guyton AC. *Textbook of medical physiology*. 8th ed. Philadelphia: WB Saunders; 1991. p. 799–801.
125. Green M, Behrendt H. Sweating capacity of neonates. Nicotine-induced axon reflex sweating and the histamine flare. *Am J Dis Child* 1969;118:725–32.
126. Behrendt H, Green M. Drug-induced localized sweating in full-size and low-birth-weight neonates. *Am J Dis Child* 1969;117:299–306.
127. Green M, Behrendt H. Drug-induced localized sweating in neonates. *Am J Dis Child* 1970;120:434–8.
128. Foster KG, Hey EN, Katz G. The response of the sweat glands of the newborn baby to thermal stimuli and to intradermal acetylcholine. *J Physiol* 1969;203:13–29.
129. Green M. Comparison of adult and neonatal skin eccrine sweating. In: Maibach HI, Boisits EK, editors. *Neonatal skin, structure and function*. New York: Dekker; 1982. p. 35–66.
130. Harpin VA, Rutter N. Sweating in preterm babies. *J Pediatr* 1982;100:614–18.
131. Green M, Behrendt H. Sweating responses of neonates to local thermal stimulation. *Am J Dis Child* 1973;125:20–5.
132. Hey EN, Katz G. Evaporative water loss in the newborn baby. *J Physiol* 1969;200:605–19.
133. Oh W, Karecki H. Phototherapy and insensible water loss in the newborn infant. *Am J Dis Child* 1972;124:230–2.
134. Jones RW, Rochefort MJ, Baum JD. Increased insensible water loss in newborn infants nursed under radiant heaters. *BMJ* 1976;2:1347–50.
135. Williams PR, Oh W. Effects of radiant warmer on insensible water loss in newborn infants. *Am J Dis Child* 1974;128:511–14.
136. Karlsson H, Hanel SE, Nilsson K, et al. Measurement of skin temperature and heat flow from skin in term newborn babies. *Acta Paediatr* 1995;84:605–12.
137. Gladman G, Chiswick ML. Skin conductance and arousal in the newborn. *Arch Dis Child* 1990;65:1063–6.
138. Hernes KG, Morkrid L, Fremming A, et al. Skin conductance changes during the first year of life in full-term infants. *Pediatr Res* 2002;52:837–43.
139. Sato S, Ogihara Y, Hiraga K, et al. Fine structure of unmyelinated nerves in neonatal skin. *J Cutan Pathol* 1977;4:1–8.
140. Cauna N. The free pacillate nerve endings of the human hairy skin. *J Anat* 1973;115:277–88.
141. Cauna N. Fine morphological characteristics and microtopography of the free nerve endings of the human digital skin. *Anat Rec* 1980;198:643–56.
142. Moll R, Moll I, Franke WW. Identification of Merkel cells in human skin by specific cyto-keratin antibodies: changes of cell density and distribution in fetal and adult plantar epidermis. *Differentiation* 1984;28:136–54.
143. Moll I, Moll R, Franke WW. Formation of epidermal and dermal Merkel cells during human fetal skin development. *J Invest Dermatol* 1986;87:779–87.
144. Narisawa Y, Hashimoto K, Nihei Y, et al. Biological significance of dermal Merkel cells in development of cutaneous nerves in human fetal skin. *J Histochem Cytochem* 1992;40:65–71.
145. Perera P, Kurban AK, Ryan TJ. The development of the cutaneous microvascular system in the newborn. *Br J Dermatol* 1970;82:86–91.
146. Mayer KM. Observations on the capillaries of the normal infant. *Am J Dis Child* 1921;22:381–7.
147. Beinder E, Trojan A, Bucher HU, et al. Control of skin blood flow in pre- and full-term infants. *Biol Neonate* 1994;65:7–15.
148. Wu PY, Wong WH, Guerra G, et al. Peripheral blood flow in the neonate. 1. Changes in total, skin, and muscle blood flow with gestational and postnatal age. *Pediatr Res* 1980;14:1374–8.
149. Norman M, Herin P, Fagrell B, et al. Capillary blood cell velocity in full-term infants as determined in skin by videophotometric microscopy. *Pediatr Res* 1988;23:585–8.
150. Jahnukainen T, van Ravenswaaij-Arts C, Jalonen J, et al. Dynamics of vasomotor thermoregulation of the skin in term and preterm neonates. *Early Hum Dev* 1993;33:133–43.
151. Risbourn B, Vural M, Kremp O, et al. Neonatal thermoregulation. *Turk J Pediatr* 1991;33:121–34.
152. Thomas K. Thermoregulation in neonates. *Neon Network* 1994;13:15–22.
153. Karlsson H, Olegard R, Nilsson K. Regional skin temperature, heat flow and conductance in preterm neonates nursed in low and in neutral environmental temperature. *Acta Paediatr* 1996;85:81–7.
154. Knobel RB, Holditch-Davis D, Schwartz TA, et al. Extremely low birth weight preterm infants lack vasomotor response in relationship to cold body temperatures at birth. *J Perinatol* 2009;29(12):814–21.
155. Holbrook KA, Underwood RA, Vogel AM, et al. The appearance, density and distribution of melanocytes in human embryonic and fetal skin revealed by the anti-melanoma monoclonal antibody, HMB-45. *Anat Embryol* 1989;180:443–55.
156. Haake AR, Scott GA. Physiologic distribution and differentiation of melanocytes in human fetal and neonatal skin equivalents. *J Invest Dermatol* 1991;96:71–7.
157. Scott GA, Haake AR. Keratinocytes regulate melanocyte number in human fetal and neonatal skin equivalents. *J Invest Dermatol* 1991;97:776–81.
158. Jimbow K, Quevedo WC, Prota G, et al. Biology of melanocytes. In: Freedberg IM, Eisen AZ, Wolff K, et al., editors. *Dermatology in general medicine*. 5th ed. New York: McGraw-Hill; 1999. p. 192–220.
159. Boissy RE. The melanocyte. Its structure, function, and subpopulations in skin, eyes, and hair. *Dermatol Clin* 1988;6:161–73.
160. Szabo G, Gerald A, Pathak MA. Racial differences in the fate of melanosomes in human epidermis. *Nature* 1969;222:1081–2.
161. Bos JD. The skin immune system: lupus erythematosus as a paradigm. *Arch Dermatol Res* 1994;287:23–7.
162. Bos JD. The skin as an organ of immunity. *Clin Exp Immunol* 1997;107:3–5.
163. Bos JD, Kapsenberg ML. The skin immune system: progress in cutaneous biology. *Immunol Today* 1993;14:75–8.
164. Streilein JW, Bergstresser PR. Langerhans cells: antigen presenting cells of the epidermis. *Immunobiol* 1984;168:285–300.
165. Dorschner RA, Lin KH, Murakami M, et al. Neonatal skin in mice and humans expresses increased levels of antimicrobial peptides: innate immunity during development of the adaptive response. *Pediatr Res* 2003;53:566–72.
166. Braff MH, Hawkins MA, DiNardo A, et al. Structure-function relationships among human cathelicidin peptides: dissociation of antimicrobial properties from host immunostimulatory activities. *J Immunol* 2005;174:4271–8.
167. Rieg S, Seeber S, Steffen H, et al. Generation of multiple stable dermacidin-derived antimicrobial peptides in sweat of different body sites. *J Invest Dermatol* 2006;126:354–65.
168. Morizane S, Yamasaki K, Kabigting FD, et al. Kallikrein expression and cathelicidin processing are independently controlled in keratinocytes by calcium, vitamin D3, and retinoic acid. *J Invest Dermatol* 2010;130:1297–306.
169. Bos JD, Zonneveld I, Das PK, et al. The skin immune system (SIS): distribution and immunophenotype of lymphocyte subpopulations in normal human skin. *J Invest Dermatol* 1987;88:569–73.
170. Hogan AD, Burks AW. Epidermal Langerhans' cells and their function in the skin immune system. *Ann Allergy Asthma Immunol* 1995;75:5–12.
171. Drijckoning M, de Wolf-Peters C, Van Der Steen K, et al. Epidermal Langerhans' cells and dermal dendritic cells in human fetal and

- neonatal skin: an immunohistochemical study. *Pediatr Dermatol* 1987;4:11–7.
172. Stingl G, Hauser C, Wolff K. The epidermis: an immunologic microenvironment. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al, editors. *Dermatology in general medicine*. 4th ed. New York: McGraw-Hill; 1993. p. 172–97.
173. Kowolenko M, Carlo J, Gozzo JJ. Histologic identification of cellular differences that may contribute to the reduced immunogenicity of transplanted neonatal versus adult skin tissue. *Int Arch Allergy Appl Immunol* 1986;80: 274–7.
174. Silvers WK. Studies on the induction of tolerance of the H-Y antigen in mice with neonatal skin grafts. *J Exp Med* 1968;128:69–83.
175. Silvers WK, Collins NH. The behavior of H-Y-incompatible neonatal skin grafts in rats. *Transplantation* 1979;28:57–9.
176. Kowolenko M, Gozzo JJ. Comparative study of neonatal and adult skin transplants in mice. *Transplantation* 1984;38:84–6.
177. Hanau D, Fabre M, Schmitt DA, et al. Appearance of Birbeck granule-like structures in anti-T6 antibody-treated human epidermal Langerhans cells. *J Invest Dermatol* 1988;90: 298–304.
178. Nestle FO, Nickoloff BJ. Dermal dendritic cells are important members of the skin immune system. *Adv Exp Med Biol* 1995; 378:111–6.
179. Romani N, Clausen BE, Stoitzner P. Langerhans cells and more: Langerin-expressing dendritic cell subsets in the skin. *Immunol Rev* 2010;234:120–41.
180. Romani N, Brunner PM, et al. Changing views of the role of Langerhans cells. *J Invest Dermatol* 2012;132:872–81.
181. Muller HK, Malley RC, McGee HM, et al. Effect of UV radiation on the neonatal skin immune system – Implications for melanoma. *Photochem Photobiol* 2008;84:47–54.
182. Narendran V, Visscher MO, Abril I, et al. Biomarkers of epidermal innate immunity in premature and full-term infants. *Pediatr Res* 2010;67(4):382–6.
183. Aksentijevich I, Masters SL, Ferguson PJ, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *N Engl J Med* 2009;360(23):2426–37.

Lesional Morphology and Assessment

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Introduction

Newborn infant skin can manifest with an extraordinary array of conditions. Neonatal cutaneous findings may indicate transitory, benign processes such as erythema toxicum neonatorum, or may represent important harbingers of internal disease or genetic alteration, as might be observed in patients with herpes simplex virus infection or incontinentia pigmenti. Dermatologic manifestations are readily visible to the clinician, and it is often more efficient to first assess lesional morphology and then focus history-taking on the basis of the observed clinical findings. The timely identification and accurate diagnosis of skin findings in the newborn infant therefore relies on combining a comprehensive history with a meticulous physical examination, as well as on a proper understanding of physiologic differences between neonatal, pediatric, and adult skin that will influence both the diagnosis and the management of skin conditions appropriate to the neonate. This chapter reviews the principles of morphologic assessment in the term and preterm infant.

Reaction patterns

An understanding of the specialized reaction patterns is outlined in [Tables 3.1–3.3](#) and [Box 3.1](#) and, in conjunction with a comprehensive history and assessment of cutaneous morphology, will aid the clinician in making the proper dermatologic diagnosis.

A comprehensive history and its impact

The comprehensive history is a vital part of any neonatal skin evaluation. In the newborn setting, this includes not only prenatal and perinatal histories but also maternal, paternal, and family medical histories ([Tables 3.1–3.2](#), [Box 3.2](#)).

PRENATAL HISTORY

Prenatal history should focus on questions about possible antenatal exposures to medications, drugs, or infections. Questions should examine the use of prescription and non-prescription medications, as well as controlled and uncontrolled substances such as tobacco, alcohol, cocaine and other illicit drugs. Certain drugs, for example phenytoin, valproic acid, coumadin, diethylstilbestrol, systemic retinoids, tetracycline derivatives, and penicillamine, are known teratogens. As substance abuse among mothers has become more prevalent, our knowledge of their effects on the fetus is expanding. Specific cutaneous features

may be observed with specific substances, as noted in fetal alcohol syndrome, where patients may manifest with short palpebral fissures, a broad flat nasal bridge, and a long upper lip with an absent or ill-defined philtrum.¹ Other cutaneous findings of substance abuse are less specific and defined, but have been linked with premature birth and fetal growth retardation and its inherent cutaneous susceptibilities.² Additional factors important in the prenatal history include maternal infections, especially within the first trimester when organogenesis occurs. The TORCH constellation of infections (toxoplasmosis, syphilis, rubella, cytomegalovirus, herpes), human papilloma virus, and human immunodeficiency virus (HIV) may have significant systemic and cutaneous effects on the infant, as addressed specifically in later chapters.

MATERNAL HISTORY

Maternal history should include age, medical history, and outcomes of prior pregnancies. Certain genetic disorders have been linked to advanced maternal age during pregnancy, particularly chromosomal abnormalities, the most frequent being Down syndrome.³ Maternal disease may have a significant impact on the developing fetus. Systemic lupus erythematosus and related collagen vascular disorders highlight neonatal diseases that occur as a result of transplacental transmission of pathogenic antibodies – in this case anti-Ro/SSA, anti-La/SSB, or U1RNP antibody may result in an infant with neonatal lupus erythematosus.⁴ Other autoimmune disorders (such as bullous disorders), as well as chronic medical conditions requiring systemic medications, are also important in assessing the newborn. Medical conditions acquired during pregnancy, such as gestational diabetes, will also affect fetal development. Previous pregnancies that resulted in spontaneous abortions may suggest X-linked dominant conditions or autosomal recessive conditions that are fatal in utero. Failure to initiate or poor progression of labor may be the first clue to X-linked ichthyosis in the infant.⁵ Polyhydramnios has been associated with trisomies, and junctional epidermolysis bullosa with associated pyloric atresia.^{6,7} Paternal history, although less significant, may be useful. Increased paternal age has been linked to chromosomal abnormalities, in particular Down syndrome, Apert syndrome, achondroplasia, and neurofibromatosis.^{8–12} Finally, a detailed family history may help identify possible congenital anomalies or genetic disorders. The pattern of affected family members may indicate a specific mode of inheritance. A history of consanguinity should be sought if recessive genetic disorders are suspected.

The history of labor and delivery should include approximate gestational dates. Premature, term, and postdate infants

present with different cutaneous examinations, and are differentially susceptible to cutaneous disease. For instance, premature infants have a higher incidence of hemangiomas; term infants are more likely to develop erythema toxicum neonatorum; and postdate infants undergo significant desquamation shortly after birth. Identification of congenital cutaneous candidiasis in a preterm infant at high risk for systemic infection will warrant a different approach from term infants, for whom the disease poses significantly less of a risk. An excessively prolonged labor may indicate X-linked ichthyosis. Premature rupture of membranes, prolonged labor, and evidence of fetal distress due to hypoxia or meconium aspiration, may predispose an infant to cutaneous infection and subsequent sepsis. Low-birthweight infants must be watched with particular vigilance for signs of septicemia. Other risk factors for sepsis include male gender and prematurity, the risk being inversely proportional to gestational age. Apnea, bradycardia, irritability, feeding intolerance, temperature instability, abdominal distension, increased respiratory effort, hypotonia, and glucose instability can be subtle early signs of sepsis. Cutaneous findings of infection may include a full or bulging fontanelle, generalized erythema, petechiae, purpura, and vasomotor instability, with poor peripheral circulation (i.e. mottling and cyanosis of the acral areas).¹³ The umbilical area, as well as central venous or

arterial catheterization sites, should be evaluated closely as potential portals of entry. Prolonged labor, abnormal presentation, and artificial extraction measures may account for petechiae, ecchymoses, and hematomas which may herald the onset of hyperbilirubinemia. In certain disorders, such as congenital malignancies (e.g., melanoma) or congenital infections (e.g., chorioamnionitis), examination of the placenta may be helpful.

Cutaneous examination and evaluation

Although historical evidence is important, the cornerstone of dermatology remains a careful, detailed cutaneous examination. This requires both visual and tactile assessment of the skin. Special precautions must be followed in the newborn nursery, especially in the intensive care unit setting. Careful handwashing or the use of newer topical broad-spectrum antimicrobial hand preparations, with removal of jewelry, must be performed to reduce the risk of nosocomial infections.^{14,15} Some infants may require incubators to maintain their temperature and fluid balance. During examination, prolonged exposure outside of the isolette can result in hypothermia. Open radiant warmers are helpful, but prolonged exposure should be avoided because open

TABLE 3.1
Primary lesions

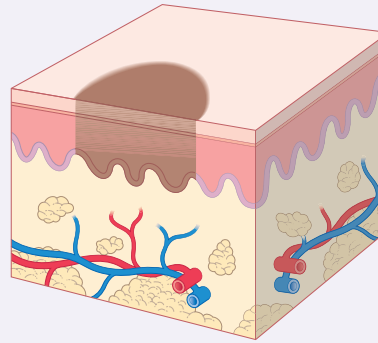
Primary lesions are defined as lesions that arise de novo and are therefore most characteristic of the disease process. The graphic representations are intended to demonstrate three-dimensional and topographic relationships and not necessarily the histology of the example shown.

MACULE

A circumscribed, flat lesion with color change, up to 1 cm in size, although the term is often used for lesions >1 cm. By definition, they are not palpable

EXAMPLES

Ash leaf macules, café-au-lait macules, capillary malformations



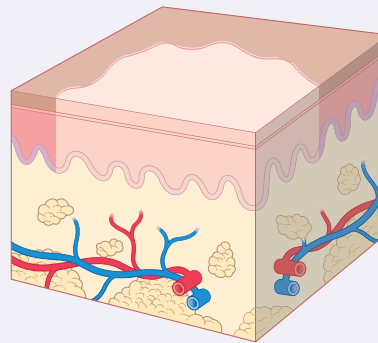
Café-au-lait macules

PATCH

A circumscribed, flat lesion with color change, >1 cm in size

EXAMPLES

Nevus depigmentosus, Mongolian spots, nevus simplex



Hemangioma precursor

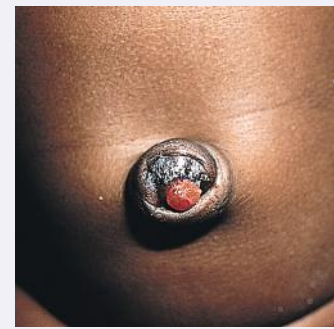
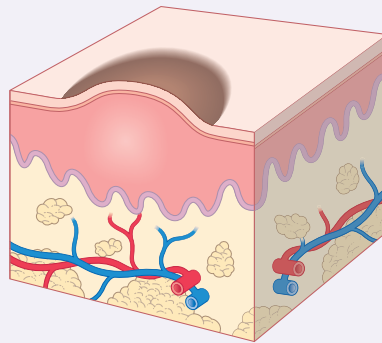
Continued

TABLE 3.1 Primary lesions (Continued)**PAPULE**

A circumscribed, elevated, solid lesion, up to 1 cm in size. Elevation may be accentuated with oblique lighting

EXAMPLES

Verrucae, milia, and juvenile xanthogranuloma



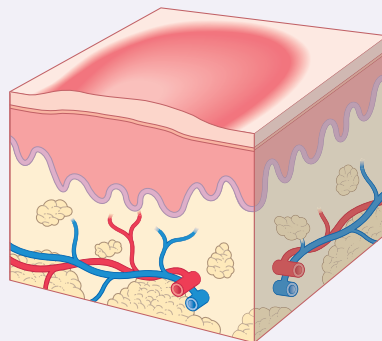
Umbilical granuloma

PLAQUE

A circumscribed, elevated, plateau-like, solid lesion, >1 cm in size

EXAMPLES

Mastocytoma, nevus sebaceus



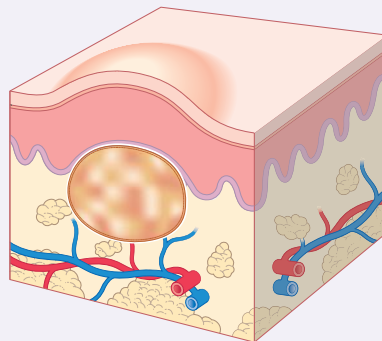
Nevus sebaceus

NODULE

A circumscribed, elevated, solid lesion with depth, up to 2 cm in size

EXAMPLES

Dermoid cysts, neuroblastoma



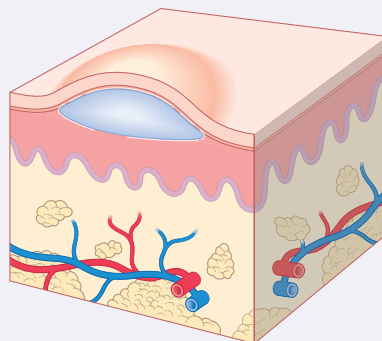
Juvenile xanthogranuloma

VESICLE

A circumscribed, elevated, fluid-filled lesion up to 1 cm in size

EXAMPLES

Herpes simplex, varicella, miliaria crystallina



Acropustulosis of infancy

Continued

warmers will increase transepidermal water loss. When examining an infant, good lighting and adequate exposure are essential. Although natural lighting is best, this is rarely available. Fluorescent lights and bilirubin lights may mask some of the subtle contours and colors of individual lesions. Where practical, the

infant should routinely have all clothing removed, including diapers, so that the entire skin surface can be examined.

A great deal of similarity may occur between pathologic processes. Although some diagnoses are obvious, there is only a finite number of ways that skin can express disease. An orga-

TABLE
3.1

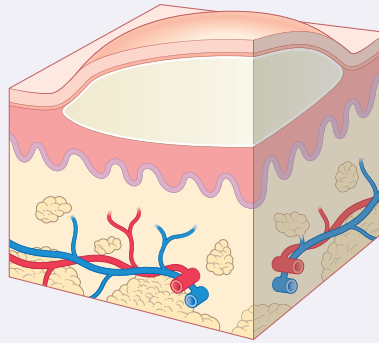
Primary lesions (Continued)

BULLA

A circumscribed, elevated, fluid-filled lesion >1 cm in size

EXAMPLES

Sucking blisters, epidermolysis bullosa, bullous impetigo



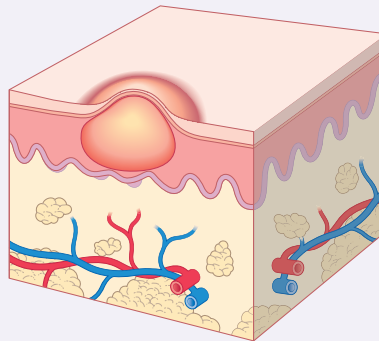
Insect bite reaction

PUSTULE

A circumscribed, elevated lesion filled with purulent fluid, <1 cm in size. Pustules can be primary skin lesions or can initially be a vesicle that then becomes filled with cells or debris.

EXAMPLES

Transient neonatal pustular melanosis, erythema toxicum neonatorum, infantile acropustulosis



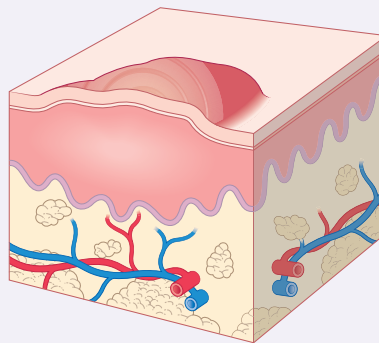
Transient neonatal pustular melanosis

WHEEL

A circumscribed, elevated, edematous, often evanescent lesion, caused by accumulation of fluid within the dermis

EXAMPLES

Urticaria, bite reactions, drug eruptions



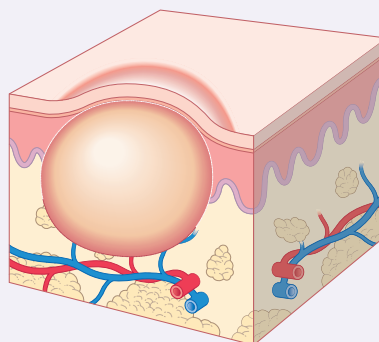
Drug eruption

ABSCESS

A circumscribed, elevated lesion filled with purulent fluid, >1 cm in size.

EXAMPLE

Pyoderma



Abscess

TABLE
3.2

Secondary lesions

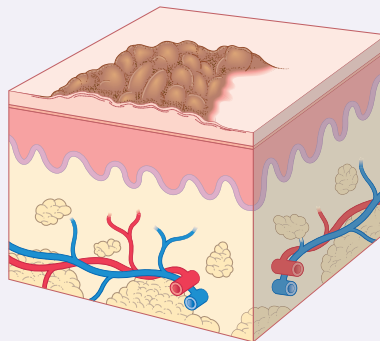
Secondary lesions are characteristically brought about by modification of primary lesions, either by the individual or through the natural evolution of the lesion in the environment. The graphic representations are intended to demonstrate three-dimensional and topographic relationships and not necessarily the histology of the example shown.

CRUST

Results from dried exudate overlying an impaired epidermis. Can be composed of serum, blood, or pus

EXAMPLES

Epidermolysis bullosa, impetigo



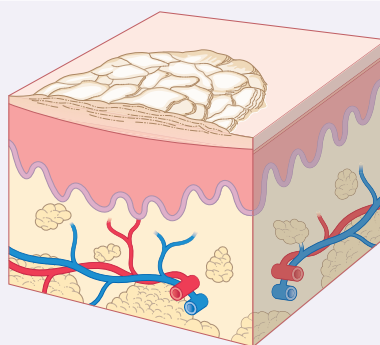
Infected atopic dermatitis

SCALE

Results from increased shedding or accumulation of stratum corneum as a result of abnormal keratinization and exfoliation. Can be subdivided further into pityriasiform (branny, delicate), psoriasiform (thick, white, and adherent), and ichthyosiform (fish scale-like)

EXAMPLES

Ichthyoses, postmaturity desquamation, seborrheic dermatitis



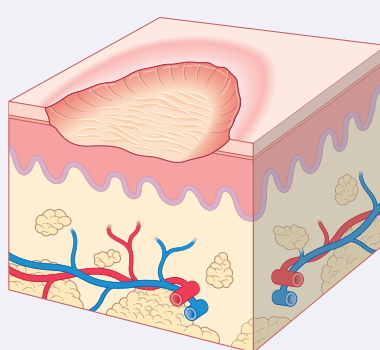
Seborrheic dermatitis

EROSION

Intraepithelial loss of epidermis. Heals without scarring

EXAMPLES

Herpes simplex, certain types of epidermolysis bullosa



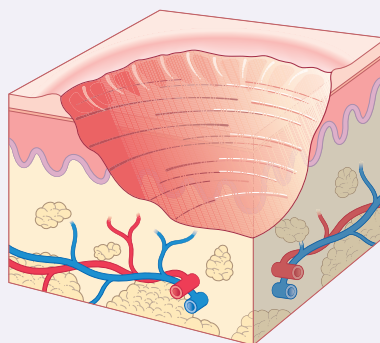
Epidermolysis bullosa

ULCER

Full-thickness loss of the epidermis, with damage into the dermis. Will heal with scarring

EXAMPLES

Ulcerated hemangiomas, aplasia cutis congenita



Aplasia cutis congenita

Continued

TABLE
3.2

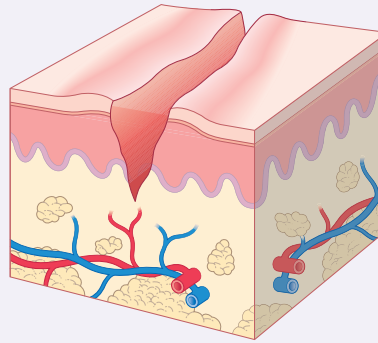
Secondary lesions (Continued)

FISSURE

Linear, often painful break within the skin surface, as a result of excessive xerosis

EXAMPLES

Inherited keratodermas, hand and foot eczema



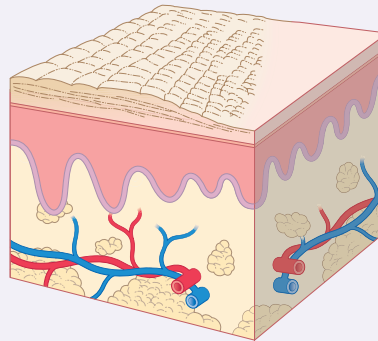
Atopic dermatitis

LICHENIFICATION

Thickening of the epidermis with exaggeration of normal skin markings caused by chronic scratching or rubbing

EXAMPLES

Sucking callus, atopic dermatitis



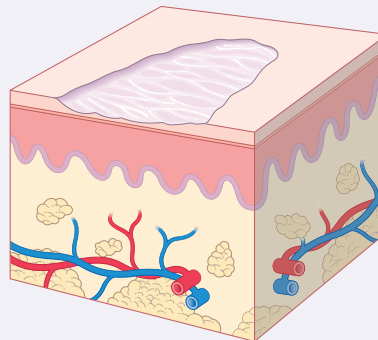
Atopic dermatitis

ATROPHY

Localized diminution of skin. Epidermal atrophy results in a translucent epidermis with increased wrinkling, whereas dermal atrophy results in depression of the skin with retained skin markings. Use of topical steroids can result in epidermal atrophy, whereas intralesional steroids may result in dermal atrophy

EXAMPLES

Aplasia cutis congenita, intrauterine scarring, and focal dermal hypoplasia



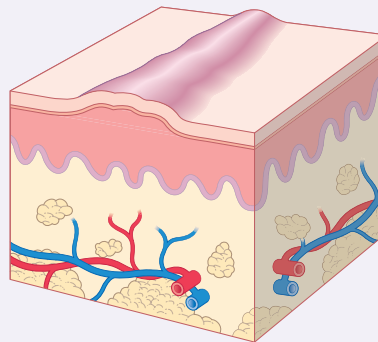
Focal dermal hypoplasia

SCAR

Permanent fibrotic skin changes that develop as a consequence of tissue injury. In utero, scarring can occur as a result of certain infections or amniocentesis, or postnatally from a variety of external factors

EXAMPLES

Congenital varicella, aplasia cutis congenita



Aplasia cutis congenita

BOX 3.1 COLOR OF LESIONS

To the untrained eye, the appreciation of subtle variations in color is often the most difficult concept to grasp. Fortunately, this assessment does not carry the diagnostic weight of the primary or secondary lesions. When evaluating the color, one must take into account the background pigmentation of the patient. In infants with darker skin type, subtle erythema or jaundice may be difficult to appreciate. Likewise, pigment dilution is more difficult to evaluate in lighter skin. The most prominent colors seen in cutaneous pathologic processes are described below.

RED

Red color can be the result of vasodilation or hyperemia caused by inflammation. Deeper red or purple hues suggest extravasation of red blood cells. Diascopy is a diagnostic maneuver to help differentiate these possibilities. By applying pressure to the lesion, one can see whether the lesion blanches, which suggests rubor due to vasodilation or inflammation. Conversely, nonblanching lesions suggest vascular damage, with consequent extravasation of blood into the dermis.

WHITE

White color can be the result of loss of pigment within the epidermis or the accumulation of white material such as purulent exudate or keratinous material. One should not use the term white to describe skin-colored lesions.

YELLOW

Yellow coloration can be seen in lipid-containing lesions such as xanthomas, or as a result of bile accumulation, as in jaundice.

BROWN/BLUE/GRAY/BLACK

Variations in color are related to increased melanin or hemosiderin in the skin. The more superficial the pigmentation, the darker the color. Melanin in the deep dermis appears blue to gray, owing to the Tyndall effect. Evaluation of hyperpigmentation and hypopigmentation must take into account the infant's genetic and racial background. Diffuse hyperpigmentation is rare and may signify systemic disease, such as congenital Addison disease and other endocrinopathies, nutritional disorders, and hepatic disease. Likewise, diffuse hypopigmentation can be seen in systemic diseases such as albinism and phenylketonuria.

BOX 3.2 MATERNAL, FAMILY, PERINATAL, AND NEONATAL HISTORY RELEVANT TO NEONATAL SKIN EVALUATION**MATERNAL AND FAMILY HISTORY**

- Parental age
- History of skin or mucous membrane disease
- History of blistering, skin fragility, ectodermal defects, or birthmarks
- History of significant systemic disease, congenital anomalies, or genetic disorders
- History of infectious diseases (e.g., herpes simplex virus, syphilis, HIV)

OBSTETRIC HISTORY

- Previous pregnancies, outcomes, miscarriages, maternal serologic status (syphilis, rubella, HIV)
- Illnesses, surgery, fever, or rash
- Medication used during pregnancy
- Prenatal testing (amniocentesis, chorionic villus sampling)
- Timing of amniotic membrane rupture
- Labor duration/complications
- Intrauterine monitoring
- Amniotic fluid (±meconium; purulence; oligohydramnios or polyhydramnios)
- Fever before or after delivery
- Fetal distress
- Delivery method (e.g., vacuum extraction, forceps, cesarean section)
- Placental abnormalities

NEONATAL HISTORY

- Gestational age, birthweight, and birthweight relative to gestational age (low, average, high)
- Resuscitation needs
- Medication – past, present
- Cutaneous history: onset, morphology, distribution, prior treatment, evolution
- Lesions/rash
- General medical/surgical history: includes structural anomalies, history of lethargy, irritability, feeding intolerance

nized approach to evaluating and describing lesions is of paramount importance.

Examination of the skin surface should proceed systematically from inspection to palpation, separating the body into segments to ensure complete evaluation. Inspection of the lesions should characterize the primary and secondary lesions; the colors involved; the borders; the configuration; and the distribution of relevant cutaneous findings. Relevant primary and secondary lesions should first be identified (Tables 3.1 and 3.2). An understanding of the significance of these primary and secondary lesions will not only help generate an appropriate differential diagnosis but also allow for concise communication of pertinent data to colleagues. We have attempted to use the most commonly used definitions for primary and secondary lesions. Unfortunately, a review of the core dermatologic textbooks and literature reveals a great deal of inconsistency among these definitions.^{16–20} Subsequently, the color, borders, configuration, and distribution of lesions are assessed (Table 3.3 and Box 3.1). When evaluating color, one should take into account the variations in different ethnic groups because background color will alter the overall color of lesions. The border should be examined for distinct or indistinct margins. Next, configuration should be assessed. Are the lesions linear, annular, nummular, targetoid, grouped, or retiform? Finally, the last step is

the evaluation of distribution. Is the lesion single or multiple, localized or generalized, symmetric or asymmetric, extensor or flexural, acral, or inverse? This is then followed by palpation of the lesion, with particular attention to the border. Lesions may be soft, firm, fluctuant, indurated, or tender.

Mucous membranes, teeth, hair, and nails should be included in a full cutaneous examination. Teeth, hair, and nails are ectodermal structures like the skin, and can be intimately linked to cutaneous pathologic processes. Teeth are normally absent at birth, but natal teeth, which represent prematurely erupted primary incisors, can be seen. Delayed onset of eruption, absent or abnormal teeth, or enamel dysplasia can be seen in the ichthyoses, ectodermal dysplasias, and other genodermatoses such as incontinentia pigmenti and tuberous sclerosis. Sparse to abundant hairs can be seen as a variation of normal. Synchronous loss of hair followed by regrowth is a normal finding until the development of an adult hair distribution, usually during the first year of life. Subtle changes in hair texture with a matted, lusterless, brittle, or unruly appearance should prompt closer evaluation by light microscopy for hair shaft abnormalities, which can be elucidated with scanning electron microscopy. Diffuse hypotrichosis can be seen in hidrotic and anhidrotic ectodermal dysplasia, ichthyoses, and incontinentia pigmenti. Diffuse hypertrichosis can be seen in mucopolysaccharidosis,

TABLE
3.3**Borders, configuration, and distribution of lesions****BORDER**

The border of a cutaneous lesion may also help in the differential diagnosis. Some lesions, such as acrodermatitis enteropathica, ichthyosis linearis circumflexa, and erysipelas, have distinct borders

EXAMPLES

Lesions with indistinct borders include cellulitis and atopic dermatitis. The borders of the lesion may be raised and indurated, as in granuloma annulare and neonatal lupus



Note the characteristically well-demarcated border in these lesions of acrodermatitis enteropathica

Configuration**LINEAR**

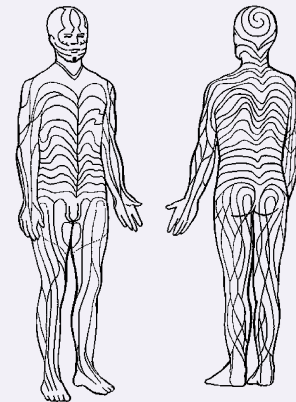
Several lesions follow a linear pattern. Linear lesions can be subdivided (see below).

BLASCHKO (LINEAR)

These linear V- and S-shaped lines are believed to represent patterns of neuroectodermal migration, and skin lesions in this distribution indicate areas of cutaneous mosaicism. They do not follow any known vascular, nervous, or lymphatic pattern

EXAMPLES

Linear epidermal nevus, incontinentia pigmenti



Linear epidermal nevus

Continued

TABLE
3.3

Borders, configuration, and distribution of lesions (Continued)

DERMATOMAL/ZOSTERIFORM (LINEAR)

Lines demarcating a dermatome supplied by one dorsal root ganglia

EXAMPLES

Herpes zoster



Herpes zoster

KOEBNERIZATION (LINEAR)

Certain skin conditions tend to recapitulate at sites of skin injury, which may give them a linear configuration. Classic examples include: psoriasis, lichen planus, and lichen nitidus

EXAMPLES

Lichen nitidus, psoriasis



Lichen nitidus

ANATOMIC LESIONS (LINEAR)

Skin lesions that occur in a linear configuration may indicate underlying involvement of a vascular structure, as might be encountered with infiltration of an intravenous cannulation site. Infectious organisms, such as *Aspergillus*, *Rhizopus*, or mycobacteria, may also spread along a vascular or 'sporotrichoid' distribution

EXAMPLES

Sporotrichosis, atypical mycobacterial infection



Iatrogenic calcinosis cutis resulting from extravasation of calcium from an intravenous catheter

EXOGENOUS (LINEAR)

If lesions are found to be discordant with normal lines of demarcation, one should search for an external insult

EXAMPLES

Allergic contact dermatitis, pressure-induced injury, non-accidental trauma



Sockline hyperpigmentation

Continued

TABLE
3.3**Borders, configuration, and distribution of lesions (Continued)**

<p>SEGMENTAL PATTERNS</p> <p>The configuration of segmental lesions is thought to be determined by the location of embryonic placodes or other embryonic territories, as can be seen in PHACE(S) syndrome</p>	<p>EXAMPLES</p> <p>Infantile hemangioma Nevus of Ota</p>	 <p>Segmental infantile hemangioma</p>
<p>SESSILE</p> <p>Papules, nodules, or tumors having a broad base</p>	<p>EXAMPLES</p> <p>Molluscum, dermatofibroma, dermal nevus, juvenile xanthogranuloma</p>	 <p>Sessile juvenile xanthogranuloma</p>
<p>PEDUNCULATED (POLYPOID)</p> <p>Papules, nodules, or tumors having a narrow, stalk-like base</p>	<p>EXAMPLES</p> <p>Skin tags (fibroepithelial polyps), lobular capillary hemangioma, condyloma</p>	 <p>Pedunculated lobular capillary hemangioma</p>
<p>ANNULAR</p> <p>A round, ring-shaped lesion, where the periphery is distinct from the center</p>	<p>EXAMPLES</p> <p>Tinea corporis, neonatal lupus, syphilis, annular erythema of infancy</p>	 <p>Annular lesions of neonatal lupus</p>
<p>NUMMULAR</p> <p>A coin-shaped lesion, with homogenous character throughout</p>	<p>EXAMPLES</p> <p>Nummular eczema, discoid lesions of neonatal lupus</p>	 <p>Nummular eczema</p>

Continued

TABLE
3.3

Borders, configuration, and distribution of lesions (Continued)

GYRATE/POLYCYCLIC/ARCIFORM/SERPIGINOUS

Variations in the spectrum of annular lesions

EXAMPLES

Neonatal lupus erythematosus, urticaria



Urticarial drug eruption

TARGETOID/IRIS

Concentric ringed lesions, often with a dusky or bullous center. This is characteristic of erythema multiforme

EXAMPLES

Erythema multiforme



Early lesions of erythema multiforme

HERPETIFORM

Clustered, similar to herpes simplex

EXAMPLES

Herpes simplex



Herpes simplex infection

CORYMBIFORM

Defined as a central cluster of lesions surrounded by scattered individual lesions

EXAMPLES

Verrucae



Verrucae ('ring warts')

RETIFORM/RETICULATE

A net-like pattern of lesions

EXAMPLES

Cutis marmorata, cutis marmorata telangiectatica congenita



Cutis marmorata telangiectatica congenita

Cornelia de Lange syndrome, and hypertrichosis lanuginosa. Nail abnormalities, in particular aplasia, hypoplasia, and dysplasia, have been associated with chromosomal disorders, ectodermal dysplasias, and epidermolysis bullosa. Absent nails or triangular lunulae have been associated with nail–patella syndrome. Finally, to complete the cutaneous examination, the lymph nodes, liver, and spleen should be palpated, particularly when infectious or neoplastic diagnoses are suspected.

Considerations unique to the neonatal period

Cutaneous reaction patterns in newborns can differ significantly from those seen in children and adults, because of the immaturity of the skin and its components. Although the precise mechanisms have not been fully elucidated, there are numerous clinical examples of such differences. Although all the known dermoepidermal junction antigens are made by the middle of the second trimester, the lack of a developed rete

ridge pattern and well-developed collagen fibrils within the papillary dermis may explain the greater propensity for vesicle formation in the newborn.²¹ The epidermis, particularly in immature infants, has a relatively thin stratum corneum, which results in increased transepidermal water loss, making infants more susceptible to xerosis. Furthermore, the immature epidermis is quite fragile and prone to trauma at sites of maceration and friction, such as the neck, axillae, and groin. Even mild adhesive can strip the epidermis, causing significant damage.²² The loss of this barrier function increases susceptibility to cutaneous infection with both bacteria and *Candida* species. The composition of neonatal subcutaneous fat, with its greater proportion of saturated fatty acids, makes it more prone to hypoxic trauma, leading to subcutaneous fat necrosis.²³ The immaturity of the cutaneous vasculature, with its exaggerated vasomotor tone in response to hypothermia, contributes to the prevalence of cutis marmorata in infancy.²⁴

Access the full reference list at [ExpertConsult.com](https://www.expertconsult.com)



REFERENCES

1. Clarren SK, Smith DW. The fetal alcohol syndrome. *N Engl J Med* 1978;298:1063–7.
2. Buchi KF. The drug-exposed infant in the well-baby nursery. *Clin Perinatol* 1998;25:335–50.
3. Hansen JP. Older maternal age and pregnancy outcome: a review of the literature. *Obstet Gynecol Surv* 1986;41:726–42.
4. McCauliffe DP. Neonatal lupus erythematosus: a transplacentally acquired autoimmune disorder. *Semin Dermatol* 1995;14:47–53.
5. Bradshaw KD, Carr BR. Placental sulfatase deficiency: maternal and fetal expression of steroid sulfatase deficiency and X-linked ichthyosis. *Obstet Gynecol Survey* 1986;41:401–13.
6. Carlson DE, Platt LD, Medearis AL. The ultrasound triad of fetal hydramnios, abnormal hand posturing, and any other anomaly predicts autosomal trisomy. *Obstet Gynecol* 1992;79:731–4.
7. Fine JD, Eady RA, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *J Am Acad Dermatol* 2008;58(6):931–50.
8. McIntosh GC, Olshan AF, Baird PA. Paternal age and the risk of birth defects in offspring. *Epidemiology* 1995;6:282–8.
9. Moloney DM, Slaney SF, Oldridge M, et al. Exclusive paternal origin of new mutations in Apert syndrome. *Nature Genet* 1996;13:48–53.
10. Zhu JL, Madsen KM, Vestergaard M, et al. Paternal age and congenital malformations. *Hum Reprod* 2005;20:3173–7.
11. Wilkin DJ, Szabo JK, Cameron R, et al. Mutations in fibroblast growth-factor receptor 3 in sporadic cases of achondroplasia occur exclusively on the paternally derived chromosome. *Am J Hum Genet* 1998;63:711–16.
12. Riccardi VM, Dobson CE 2nd, Chakraborty R, et al. The pathophysiology of neurofibromatosis: IX. Paternal age as a factor in the origin of new mutations. *Am J Med Genet* 1984;18:169–76.
13. Fanaroff AA, Korones SB, Wright LL, et al. Incidence, presenting features, risk factors and significance of late onset septicemia in very low birth weight infants. *Pediatr Infect Dis J* 1998;17:593–8.
14. Baltimore RS. Neonatal nosocomial infections. *Semin Perinatol* 1998;22:25–32.
15. Gaynes RP, Edwards JR, Jarvis WR, et al. Nosocomial infections among neonates in high-risk nurseries in the United States. *Pediatrics* 1996;98:357–61.
16. Fitzpatrick TB, Bernhard JD. Dermatologic diagnosis by recognition of clinical morphologic patterns. In: Fitzpatrick TB, Eisen AZ, Wolff K, et al, editors. *Dermatology in general medicine*, vol. 1. 4th ed. New York: McGraw Hill; 1993. p. 55.
17. Hurwitz S. An overview of dermatologic diagnosis. In: Hurwitz S, editor. *Clinical pediatric dermatology*. 2nd ed. Philadelphia: WB Saunders; 1993. p. 1.
18. Jackson R. Definitions in dermatology. A dissertation on some of the terms used to describe the living gross pathology of the human skin. *Clin Exp Dermatol* 1978;3:241–7.
19. Lewis EJ, Dahl MV. On standard definitions: 33 years hence. *Arch Dermatol* 1997;133:1169.
20. Ashton RE. Standard definitions in dermatology: the need for further discussion. *Arch Dermatol* 1998;134:637–8.
21. Solomon LM, Esterly NB. Neonatal dermatology. I. The newborn skin. *J Pediatr* 1970;77:888–94.
22. Harpin VA, Rutter N. Barrier properties of the newborn infant's skin. *J Pediatr* 1983;102:419–25.
23. Hicks MJ, Levy ML, Alexander J, et al. Subcutaneous fat necrosis of the newborn and hypercalcemia: case report and review of the literature. *Pediatr Dermatol* 1993;10:271–6.
24. Smales OR, Kime R. Thermoregulation in babies immediately after birth. *Arch Dis Child* 1978;53:58–61.

Skin of the Premature Infant

ERIN F. MATHES | MARY L. WILLIAMS

Introduction

The premature infant assumes the challenge of postnatal life, despite the immaturity of essential functions. Skin functions are primarily protective, and immaturity of the skin contributes to the vulnerability of the preterm infant. The main function of the skin is to provide a permeability barrier that both protects the aqueous interior of the infant from desiccation in the xeric atmosphere and prevents massive influx of water when immersed in hypotonic solutions.¹ Other important functions of skin include barriers to percutaneous absorption of exogenous xenobiotics, to injury from mechanical trauma, to colonization and penetration by microorganisms, and to injury from ultraviolet light. In addition to its barrier functions, skin also participates in the thermoregulatory, neurosensory, and immunologic systems.

The consequences of skin immaturity for the premature infant depend on the infant's position on the maturational timetable for each cutaneous function, which is in turn dependent on the infant's gestational and postnatal ages. All skin layers (i.e. epidermis, dermis, and subcutaneous fat) are thinner in the preterm infant than at term (Table 4.1).² Because the outermost layers of the epidermis (i.e. the stratum corneum) are the primary effectors of most of the barrier properties of skin, the timetable for maturation of the stratum corneum predicts the competence of many skin functions. Stratum corneum begins to form around hair follicles at about 14 weeks' gestational age and spreads to include the epidermis between hair follicles by 22–24 weeks' gestational age (see Table 1.2). During the ensuing weeks, the thickness of the stratum corneum increases from only a few to several cell layers,² such that by term, it is actually thicker than adult stratum corneum. The 'excess' outermost layers of stratum corneum are then shed during the first days of life; this process of physiologic desquamation is accentuated in postmature babies. Another component of fetal skin, the vernix caseosa (a complex proteolipid material) is formed in part by sebaceous gland secretions beginning at about 28 weeks' gestational age. The percentage surface area covered with vernix peaks at 33–37 weeks' gestational age, then decreases in full-term and post-term infants. Its functions may include roles in temperature regulation, permeability barrier, and innate immunity.³

The histologic features described above underlie the clinical characteristics of skin maturation embodied in the Ballard scale (see Table 1.5) widely used for assessing gestational age.⁴ In the extremely premature infant (<24 weeks), the skin is sticky, friable, and transparent (Fig. 4.1); lanugo hairs are absent. As gestation progresses, the skin becomes less transparent, and peeling and surface cracking are increasingly seen, indicative of a thickening stratum corneum, and lanugo hair density peaks and then regresses. Despite definition of these milestones of gross and microscopic skin development, with the exception of

the permeability barrier, little is known about the competency or developmental timetable of most skin functions in premature infants.

The permeability barrier in the preterm infant

The permeability barrier resides in the stratum corneum through its provision of a hydrophobic lipid shield over the underlying nucleated cell layers.¹ Because of their plasma and intracellular membranes, most cells are hydrophobic relative to the vascular and extracellular compartments; however, in the stratum corneum this pattern is reversed. Instead, the extracellular compartment of the stratum corneum is filled with a highly organized series of hydrophobic lipid membranes in the extracellular spaces, whereas the anucleate corneocytes form an aqueous compartment as a result of loss of their plasma and organelle membranes. This interposition of hydrophobic lipid membranes in the extracellular compartment retards the movement of water inward or outward across the stratum corneum. The stacking of multiple layers of cornified cells surrounded by extracellular lipid bilayers further enhances this barrier to water movement, through the generation of a tortuous intercellular pathway for water movement.

As a multilayered stratum corneum develops in the third trimester,² the barrier to transepidermal water loss (TEWL) also matures, such that by 34 weeks' gestation TEWL rates approximate adult values.^{5,6} Barrier competence can be measured non-invasively by a variety of direct and indirect means.^{7–9} By all of these measures, the extent of permeability barrier immaturity parallels the degree of prematurity. In addition to increasing stratum corneum thickness, the development of a competent permeability barrier in fetal rat skin is accompanied by (1) deposition of neutral lipid in the intercellular domains of stratum corneum; (2) increasing stratum corneum cholesterol and ceramide content; and (3) the organization of these lipids into mature lamellar membrane structures, as viewed by electron microscopy.^{10,11} Whether these same lipid biochemical and ultrastructural changes also underlie barrier formation during human skin development has not yet been determined, but a large body of evidence from other sources predicts that this will be the case.

Permeability barrier maturation accelerates after birth, such that by 2–3 weeks' postnatal age, most premature infants, regardless of gestational age, have competent barriers.⁶ Thus, maturation that may require approximately 10 weeks to complete in utero is accelerated following premature delivery. However, as the limits of viability have been lowered to include survivors of 25 weeks' (<750 g) to even 22 weeks' gestational age, barrier function may take as long as 8 weeks following birth, to mature.^{12,13} The gestational ages of these very immature infants

TABLE
4.1

Comparative features of premature, newborn, and adult skin

	Premature	Newborn	Adult
Skin thickness	0.9 mm	1.2 mm	2.1 mm
Epidermal surface	Vernix (gelatinous)	Vernix	Dry
Epidermal thickness	~20–25 μ m	~40–50 μ m	~50 μ m
Stratum corneum thickness	4–5 μ m	9–10 μ m	9–15 μ m
Spinous cell glycogen content	5–6 cell layers	>15 cell layers	>15 cell layers
Melanocytes	Abundant	Little or none	Little or none
	High number of cells; few mature melanosomes	Similar number of cells to young adult; low melanin production	Numbers decrease with age; melanin production dependent on skin type, body area
Dermal–epidermal junction	All known adult antigens expressed; fewer and smaller desmosomes	Structural features and antigens similar to those of the adult	Well-developed adhesive structures; large number of antigens expressed
Papillary dermis			
Boundary with reticular dermis	Present but not marked	Present but not marked	Marked
Size of collagen fiber bundles	Small	Small	Small
Cellular density	Abundant	Abundant	Moderately abundant
Reticular dermis			
Boundary with the subcutis	Marked	Marked	Marked
Size of collagen fiber bundles	Small	Small to intermediate	Large
Cellular density	Abundant	Moderately abundant	Sparse
Elastic fibers	Sparse; tiny with immature structure	Small size and immature structure; distribution similar to adult	Large in reticular dermis, small and immature in papillary dermis; form network
Hypodermis	Well-developed fatty layer	Well-developed fatty layer	Well-developed fatty layer

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Figure 4.1 Skin of an extremely premature infant (<24 weeks). Note the moist, glistening, translucent surface of this very low birth-weight infant's hand reflecting an impaired barrier to TEWL. (Courtesy of Cynthia Jensen, RN.)

directly coincide with the timetable for stratum corneum formation (see above). It may not be surprising, therefore, that extremely premature infants do not respond as rapidly to maturational signals initiated by birth. In fetal rat skin, it is air exposure with evaporation of water from the skin surface that stimulates accelerated barrier formation, because this acceleration can be prevented by covering the skin surface with a vapor-impermeable membrane.¹⁴ The accelerated postnatal development of human preterm skin may also be prevented if it is covered with occlusive materials or exposed to a humid environment.^{15,16}

Permeability barrier ontogenesis is developmentally regulated; hence, small-for-dates infants exhibit a barrier function that is appropriate for their gestational age.¹⁷ In fetal rats, barrier

maturation is regulated by glucocorticoids,¹⁸ thyroid hormone, and sex hormones, as well as by activators and ligands of the PPAR α and LXR nuclear hormone receptors (Table 4.2).¹¹ Some of these agents also regulate lung development; and glucocorticoids often are administered prepartum to mothers to accelerate fetal lung maturation when premature delivery is imminent.¹⁹ Whether barrier maturation is also stimulated by these interventions in humans is presently uncertain. One group demonstrated that preterm infants of mothers treated with glucocorticoids have reduced insensible water losses and lower serum sodium concentrations in the first 4 days of life, consistent with a maturational effect on the skin barrier.²⁰ In contrast, Jain and colleagues²¹ reported that epidermal maturation and barrier function did not appear to be influenced by antenatal steroids.

Another aspect of the permeability barrier that undergoes postnatal maturation is the 'acid mantle'. An acidic pH within the stratum corneum is required for normal permeability barrier homeostasis and for stratum corneum integrity and cohesion. At birth, human stratum corneum has a near-neutral surface pH. This pH declines over the ensuing days to weeks to become acidic, comparable with that of adults. Complete acidification may not occur until 3–6 months of age in term infants.²² Whether this maturation is further delayed in preterm infants is unknown.^{23–25}

Consequences of permeability barrier immaturity

FLUID AND ELECTROLYTE IMBALANCE AND EVAPORATIVE ENERGY LOSS

The primary consequences of permeability barrier immaturity are: (1) increased evaporative loss of free water from the skin surface, placing the infant at risk for volume depletion, particularly hyponatremic dehydration; and (2) energy loss through

TABLE 4.2 Regulatory signals for skin barrier formation in fetal rats

Activator	Effect	Nuclear receptor	Class
Dexamethasone	Accelerate	Glucocorticoid	I
Thyroid hormone	Accelerate	Thyroid hormone	II
Diethylstilbestrol	Accelerate	Estrogen	I
Testosterone	Retard	Androgen	I
Linoleic acid	Accelerate	PPAR α	II
Clofibric acid	Accelerate	PPAR α	II
Farnesol	Accelerate	?FXR or PPAR α	II
25-hydroxycholesterol	Accelerate	LXR	II
Ciglitazone prostaglandin J ₂	No effect	PPAR γ	II
GW-1514 (free fatty acids)	Accelerate	PPAR- β/Δ	II

Class I: Steroid hormone receptors. Ligand binds in cytosol, translocates to nucleus after ligand binding; regulates gene transcription as homodimer.

Class II: RXR-interacting subfamily of receptors. Ligand binds to receptor in nucleus; regulates gene transcription as heterodimer with the RXR receptor and its ligand, 9-cis retinoic acid (e.g., RXR-T3R; RXR-Vitamin D3R).

heat of evaporation; that is, 0.58 kilocalories (kcal) are expended for each milliliter (mL) of water that evaporates.²⁶ Therefore, optimal care of the premature infant requires both accurate compensation for cutaneous water losses to preserve fluid and electrolyte balance, and maintenance of the infant in a thermally neutral environment, such that caloric intake can be directed toward growth and not heat production.²⁶ Although concurrent cutaneous water losses can be measured directly (i.e. by measuring TEWL), this procedure is not standard practice in most nurseries. Instead, cutaneous water losses and respiratory fluid losses are together considered insensible (i.e. not directly measured). In term infants, TEWL accounts for approximately two-thirds of insensible losses; but cutaneous water losses are much higher in preterm infants, whereas respiratory fluid losses remain relatively constant.^{27,28} Neonatal fluid requirements are estimated using complex formulas that take into account the following:

- Measured losses in urine and feces
- Estimates of insensible losses
- Requirements to support growth (increasing with post-gestational age).

Neonatal fluid requirements must be modified by postnatal age to compensate for fluid redistribution (i.e. requirements on the first extrauterine day are decreased as a result of contraction of the extracellular compartment). There is also considerable variability in TEWL among preterm infants of the same gestational and post-gestational ages; moreover, barrier maturation is often quite precipitous.^{7,12} Fluid replacements are also adjusted as needed to compensate for excessive weight loss or gain and/or for serologic parameters of fluid or electrolyte imbalance. This inevitably results in 'chasing fluids'. While the foregoing describes usual nursery practices, it is important to bear in mind that cutaneous fluid losses are not inherently insensible (i.e. unmeasurable). Indeed, it has been shown that measurement of TEWL using rapid and noninvasive instrumentation from as few as three body sites permits accurate estimation of total cutaneous losses in preterm infants.²⁹ Despite this, measurement of TEWL has not been adopted widely by intensive-care nurseries in the approach to fluid management.

Fluid replacements must be adjusted for a number of environmental conditions (Table 4.3), because cutaneous losses are not merely a function of stratum corneum maturity. They are also modified by the ambient temperature and humidity, since both affect the vapor pressure of water at the skin surface.¹⁷

TABLE 4.3 Factors modifying cutaneous water losses in preterm infants

Factor	Effect on TEWL
Decreasing gestational age	Increased TEWL; rates proportional to degree of prematurity
Increasing postnatal age	TEWL decreases towards mature rates: >1000 g, mature by 2–3 weeks; <1000 g, mature by 4–8 weeks
Increasing ambient temperature	Increased TEWL; proportional to increase in temperature
Increasing ambient humidity	Decreased TEWL; proportional to increased humidity
Radiant warmer	Increased TEWL (by 40–100%)
Radiant warmer with heat shield	Increased TEWL (by 20–40%)
Phototherapy	Increased (by up to 50%)
Skin diseases (absent or abnormal stratum corneum)	Increased; depends on percent body surface involved and severity of defect

Phototherapy for hyperbilirubinemia also increases TEWL³⁰ and fluid requirements, particularly when white light systems are used.^{31–33} Many skin disorders also adversely affect the competence of the permeability barrier (see below and Table 4.3).

Strategies for minimizing fluid and evaporative energy losses

A humidified incubator (Fig. 4.2) can provide a thermally neutral environment with low rates of evaporative water loss, because at a relative humidity of 80% or more, skin surface evaporation effectively ceases.^{16,34,35} Scrupulous antisepsis, however, is required to prevent bacterial colonization of this environment, particularly with water-loving organisms such as *Pseudomonas* spp. Moreover, these devices obstruct access to extremely ill or unstable infants. Therefore, these infants are commonly cared for on an open bed, where a radiant warmer provides a thermally neutral environment at the expense of greatly increased rates of TEWL.^{34,36,37} Infants requiring care under radiant warmers are typically the youngest and most premature; that is, the population with the poorest skin barriers. Newer hybrid beds with a radiant warmer and humidifier allow for easy access to and observation of infants.³⁵ Use of a plastic cover or plastic bubble blanket may increase the



Figure 4.2 Preterm infant in a humidified incubator (opened for purposes of photograph). (Courtesy of Cynthia Jensen, RN.)

humidity and mitigate to some extent, the adverse effects of the radiant heating on TEWL.^{38–42} Although these plastic shields are widely employed, standards for thermal stability and transmission have not been established.⁴³

Other strategies to reduce TEWL in the preterm infant include the use of protective skin dressings or ointments. Semi-permeable dressings (e.g., Bioclusive®, Omniderm®, Opsite®, Tegaderm®) that permit some passage of water vapor and other gases, but are impervious to water and microorganisms, can reduce TEWL rates and also are protective against the trauma caused by adhesives from monitors.^{40,44–47} Moreover, barrier maturation is not inhibited by these dressings, and neither have increased rates of infection nor colonization by microorganisms been observed. Nonetheless, increased bacterial colonization under such dressings is observed in other clinical settings⁴⁸ and remains a serious consideration with their use on preterm infants. In addition, many of these dressings contain adhesive materials, and even those without adhesives can cling to the moist skin surface of the preterm newborn and injure the epidermis, unless they are either removed carefully or allowed to detach spontaneously. Furthermore, partial body applications (i.e. trunk and abdomen) to very immature infants (<1000 g), may not be sufficient to reduce total fluid requirements.⁴⁴ These limitations hinder the widespread adoption of artificial dressings in routine skin care. Because the benefits of these agents have only been shown in studies with small numbers of subjects, confirmation in larger cohorts is required before their routine use can be generally recommended.⁴²

Topical ointments, such as petrolatum⁴⁹ or Aquaphor^{®50,51} reduce TEWL, although the effect from a single application lasts only 4–8 h.^{50–52} Less frequent applications do not decrease fluid requirements, but they appear to improve the overall condition of the skin and protect against skin trauma.⁵⁰ Although largely composed of nonphysiologic lipids (e.g., long-chain hydrocarbons and wax esters), these emollients have a long history of dermatologic use without associated toxicity or evidence of significant percutaneous absorption. Nonetheless, internal hydrocarbon accumulations (paraffinomas) are reported, albeit rarely.^{53,54} Hence, the possibility remains that these lipids may not be entirely innocuous when applied to the skin of very premature infants (see also Chapter 5). A systematic review of

randomized controlled trials comparing prophylactic application of topical ointment in preterm infants to routine skin care⁵⁵ reported that daily application of topical ointment increases the risk for coagulase-negative staphylococcal and nosocomial infections in these patients. Therefore, routine application of topical ointments is no longer recommended for premature infants. However, this should not necessarily be extrapolated to developing countries. Circumstances may be very different in these settings: survival of preterm infants is much lower, care practices differ, and the morbid risks divergent. Indeed, sunflower seed oil and Aquaphor® have been shown to reduce the incidence of nosocomial infections in Bangladesh and Egypt.^{56–58} An alternative approach to barrier fortification in these infants would be use of mixtures of lipids physiologic to the skin. The extracellular membranes of the stratum corneum that provide the barrier to TEWL comprise an approximately equimolar mixture of ceramides, long-chain free fatty acids, and cholesterol.⁵⁹ The effect of various mixtures of these physiologic lipids on permeability barrier function has been examined in mature skin in experimental systems, as well as in aged skin and in some skin disorders.^{59–61} Recent studies in animal and adult human models suggest that in addition to improving epidermal hydration, vernix-based creams may improve the rate of barrier recovery from injury.^{3,62} Yet, despite the theoretic advantages of employing either physiologic lipid mixtures, or vernix-based creams, these formulations have not been examined for efficacy in treating the barrier immaturity of the preterm infant.

INCREASED PERCUTANEOUS ABSORPTION OF XENOBIOTICS

Another direct consequence of skin barrier immaturity is the increased absorption of topically applied substances (Table 4.4), sometimes with tragic consequences (see Chapter 5).^{43,63–65} This vulnerability was first recognized historically when preterm infants developed methemoglobinemia through the absorption of aniline dyes in the laundry marks placed on diapers.⁶⁶ Subsequently, the demonstration of neurotoxicity due to percutaneous absorption of hexachlorophene, a commonly used antibacterial cleanser,⁶⁶ led to wider recognition of the vulnerability of the preterm infant to toxicity from topically applied agents.

The same factors that determine the movement of water from inside out also regulate the movement of low molecular weight substances from outside in.⁶⁵ In mature skin, small (<800 Da) hydrophilic molecules are effectively excluded by the extracellular membrane system from penetration across a mature stratum corneum, whereas small hydrophobic molecules or those with amphipathic properties (containing both hydrophilic and hydrophobic parts) are able to penetrate.^{1,67} In the preterm infant, the thinner stratum corneum results in a reduction in the length (tortuosity) of the intercellular pathway, which would enhance percutaneous absorption of hydrophilic molecules. It is likely that there are also qualitative changes in the lipid composition and/or structural integrity of the lipid bilayers of immature stratum corneum that may further alter its permeability function.

In addition to immaturity of the permeability barrier, several other factors in premature infants may contribute to toxicity from topical xenobiotics.^{64,66} First, the surface area/volume ratio is increased in all infants, but even more so in premature infants;

TABLE
4.4

Hazardous or potentially hazardous compounds that may be absorbed across the skin of preterm infants (see also Chapter 5).

Compound	Toxicity	Sources
Alcohol (methylated spirits)	Skin necrosis, neurotoxic	Topical antiseptic, vehicle for topical medications/products
Aluminum ^a	Neurotoxicity	Metal containers for topical ointments
Aniline dyes	Methemoglobinemia	Laundry marks (historical)
Boric acid, borax	Shock, renal failure	Antifungals, talc powders
Benzocaine	Methemoglobinemia	Topical analgesics; teething products
Benzethonium chloride ^a	Carcinogen	Antiseptic soap
Benzyl benzoate ^a	Neurotoxicity	Scabicide
Bicarbonate	Metabolic alkalosis	Baking soda for diaper dermatitis
Camphor ^a	Gastrointestinal toxin, neurotoxicity	Topical antipruritic; camphorated oils (VapoRub [®] ; Campho-Phenique [®])
Coal tars ^a	Carcinogen	Topical anti-inflammatory products
Chlorhexidine gluconate	Skin necrosis	Topical antiseptic
Corticosteroid	Adrenal suppression, hyperadrenocorticism	Topical corticosteroids
Diphenhydramine	Neurotoxicity	Topical analgesics (Caladryl [®])
Epinephrine	High output failure	Topical vasoconstriction
Gentian violet	Possibly carcinogenic	Antimicrobial
Glycerin ^a	Hyperosmolarity	Emollients; cleansers (Aquanil [®])
Hexachlorophene	Neurotoxicity	Antiseptic soaps (pHisoHex [®]) (historical)
Iodochlorhydroxyquin	Optic neuritis	Topical antibiotic (Vioform [®])
Imidazoles	Drug interactions secondary to p450 inhibition	Topical antifungal medications: ketoconazole, miconazole, clotrimazole (Lotrimin [®])
Isopropyl alcohol	Skin necrosis; neurotoxicity	Topical antiseptics
Lactic acid ^a	Metabolic acidosis	Topical keratolytics (Lac-Hydrin [®])
Lindane	Neurotoxicity	Scabicide (Kwell [®])
Mercury	Neurotoxicity; acrodynia; nephrotic syndrome	Disinfectants; teething powder (historical)
Methylene blue	Methemoglobinemia	Vital stain (historical)
Neomycin	Ototoxicity	Topical antibiotic (Neosporin [®])
Nystatin ^a	Nephrotoxicity	Topical antifungal (Mycostatin [®])
Phenol	Cardiac and neurotoxicity	Disinfectants (e.g., commercial laundries); local anesthetic/antimicrobials (e.g., Castellani's paint)
Propylene glycol ^a	Hyperosmolarity; neurotoxicity	Topical vehicles; emollients, cleansers (Cetaphil [®])
Povidone-iodine	Skin necrosis; hypothyroidism	Topical antiseptic (Betadine [®])
Prilocaine	Methemoglobinemia	Topical anesthetic (EMLA [®])
Resorcinol	Methemoglobinemia	Topical antiseptic
Salicylic acid	Salicylism	Topical keratolytics
Silver sulfadiazine	Kernicterus; argyria	Topical antibiotic (Silvadene [®])
Sulfur ^a	Paralysis; death	Scabicide ointment
Triclosan ^a	Neurotoxicity	Topical antiseptic
Urea	Elevated BUN	Topical keratolytics/emollients

^aPotentially hazardous compounds.

this effectively increases the absorptive surface while reducing the volume of distribution for the absorbed drug. Once absorbed, reduced levels of serum-binding proteins, such as albumin, may increase the proportion of free drug. Similarly, the relative lack of an adipose reservoir to buffer against the redistribution of fat-soluble drugs, such as lindane, to lipid-enriched neural tissues, may make the premature infant particularly vulnerable to central nervous system (CNS) toxicity from such agents. Immaturity of detoxification mechanisms, such as hepatic conjugation and renal function, also alters drug pharmacodynamics and can increase toxicity.

The increased permeability of premature skin to small hydrophilic molecules has also been exploited to enhance the percutaneous delivery of medications such as theophylline.^{64,88} A confounding factor in developing transdermal delivery systems for the premature infant is their variability of barrier competence, particularly during postnatal maturation.

Clinical implications of increased percutaneous absorption of xenobiotics

In the care of the preterm infant, it is safest to assume that any medication applied to the skin may be absorbed systemically.

As a corollary, the ideal topical medications for preterm infants are those with low systemic toxicity. It is also necessary to consider the composition of the vehicle used for topical drug delivery, because some components may also be absorbed across the immature skin barrier (see Chapter 5).⁴³ The provision of a safe skin antiseptic is a particularly problematic issue, especially in the care of the most immature infants, who both have the most immature skin and are the most unstable, and therefore need repeated applications of antiseptics for intravenous access.⁶⁸ Topical iodine-containing antiseptics (10% povidone-iodine) have been largely replaced by chlorhexidine-containing antiseptics (0.5% chlorhexidine gluconate solutions) in the neonatal intensive-care nursery because of their potential for transient hypothyroxinemia and hypothyroidism due to systemic iodine absorption.^{69,89} Yet chlorhexidine-induced skin injury is also reported,^{70–72,90} with both aqueous and alcoholic vehicles. While chlorhexidine in alcohol provides better antiseptics than either ingredient alone,⁹¹ alcohol itself poses a risk for percutaneous absorption and skin necrosis in the premature neonate, especially when used under occlusion.^{71,73,74,90} Avoiding pooling of the antiseptic on the skin and wiping it off with normal saline after the procedure may help prevent chemical burns.⁹⁰

IMPACT OF PERMEABILITY BARRIER IMMATURITY ON OTHER ORGAN SYSTEMS

Excluding congenital malformations and genetic diseases, the major causes of morbidity and mortality in premature infants are: respiratory distress syndrome leading to bronchopulmonary dysplasia (BPD); patent ductus arteriosus (PDA); necrotizing enterocolitis (NEC); periventricular/intraventricular hemorrhage (IVH); and overwhelming infection. Maintenance of normal blood pressure and 'optimal' blood volume protects against these major causes of morbidity and mortality in the preterm infant, and cutaneous fluid losses are perhaps the most important destabilizing factor in fluid homeostasis of the premature infant. For example, overhydration contributes to the development of symptomatic PDA,⁹² as larger blood volumes increase shunting through the ductus arteriosus. Conversely, systemic hypotension may increase the likelihood of an intracranial hemorrhage. Alterations in cerebral blood pressure induce hemorrhage into the periventricular germinal matrix, a gelatinous and highly vascular fetal structure, which is present up to 34 weeks' gestational age.⁹³ The period of greatest risk for IVH is in the first week of life, particularly the first 2 days, which coincides not only with the time of greatest permeability barrier incompetence but also with the time when tissue fluids undergo redistribution with contraction of the extracellular fluid compartment.⁹⁴ Similarly, bronchopulmonary dysplasia is associated with increased total fluid intake in the first few days of postnatal life and increased time of ventilator use.⁹⁵ Kim and colleagues recently found that extremely low birthweight infants cared for in humidified incubators had decreased fluid intake, improved electrolyte imbalance and a lower rate of severe bronchopulmonary dysplasia.³⁵ Thus, to the extent that BPD, IVH, and PDA are precipitated by fluctuations in systemic blood pressure, overcompensated or uncompensated cutaneous water losses may be an exacerbating factor.

The pathogenesis of NEC is attributed to a triad of ischemia, oral feeding, and infection,^{96,97} each of these pathogenic factors may be exacerbated by skin immaturity. As in PDA, IVH, and BPD, fluid imbalance resulting from skin immaturity could be a cofactor, as both overcorrection of fluids⁹⁸ and hypotensive ischemia-reperfusion injury⁹⁹ are implicated in NEC. Early initiation of oral feeds¹⁰⁰ is undertaken to reverse a negative energy balance in the preterm infant. Caloric losses caused by increased evaporative water loss from the skin surface in all likelihood contribute to this caloric drain.

It seems likely, therefore, that efforts to closely monitor cutaneous losses through direct measurements of TEWL, with the goal of tight control of replacement fluids, would decrease the incidence and severity of these major complications of prematurity and improve the outcome of these infants.¹⁰¹

Immaturity of other skin barriers

CUTANEOUS BARRIER TO MECHANICAL INJURY

The skin of the premature infant is much more vulnerable to mechanical injury than that of term infants. In addition to a thinner stratum corneum, the epidermal-dermal interface lacks interdigitations (i.e. rete ridges or dermal papillary projections),¹⁰² resulting in a decreased resistance to shear forces (Table 4.1). The dermis is also thinner, less collagenized, and more gelatinous. Although the major structural proteins that

underlie the mechanical strength of skin are expressed by mid-gestation, they may not be as abundant or organized into functionally mature units as in adult or even term infants' skin.¹⁰² Skin fragility is a major problem in the care of the preterm infant. They are vulnerable to abrasions and deeper wounds from the use of adhesive tapes to secure monitors, airways, and intravenous lines (see Fig. 4.3B; see also Chapter 8). Similarly, the threshold for irritant contact dermatitis from fecal contact (diaper dermatitis), for chemical burns from prolonged contact with antiseptics,⁹⁰ or for thermal burns is much reduced.¹⁰³ Gentle handling, minimal use of adhesives coupled with substitution of hydrophilic gel¹⁰⁴ or pectin barrier¹⁰⁵ adhesives only when required, and the use of adhesive removers,¹⁰⁶ can minimize these injuries. A regimen of emollient lubrication or use of nonadherent, semipermeable dressings may also help protect against mechanical injuries (see above).

CUTANEOUS BARRIER TO INFECTION

Although mature skin is colonized by a variety of bacteria and other microorganisms, these organisms are effectively excluded from the interior. The basis for the barrier to transcutaneous infection includes both provision of a mechanical shield against invading microorganisms and specific components, such as certain lipids^{107,108} and antimicrobial peptides (defensins and cathelicidins) in the stratum corneum, that inhibit the growth of microorganisms and modulate immune responses.¹⁰⁹ The thinner, easily abraded stratum corneum of the preterm infant constitutes an impaired mechanical shield against the ingress of microorganisms. In addition, specific biochemical components of the cutaneous barrier to infection may also be immature in preterm infants. Extremely preterm infants also lack the initial protection of antimicrobial peptides in vernix caseosa.^{3,110} The contribution of the vernix to the antimicrobial barrier is unknown.

Preterm infants' skin is colonized soon after birth with coagulase-negative staphylococci, predominantly *S. epidermidis*. Colonization with *Malassezia* and *Propionibacterium* occurs later, after 3 weeks,¹¹¹ coincident with the maturation of the permeability barrier. *S. epidermidis* has become the most frequent cause of postnatally acquired systemic infections in these infants.^{112–115} *Malassezia*, as well as the opportunistic fungi *Aspergillus*, *Candida*, and *Rhizopus*, are also systemic pathogens in this group.^{116–119} Direct invasion across the immature epidermis by fungi of low pathogenicity in very preterm infants has been documented,¹²⁰ although exploitation of a portal of entry, such as site of skin injury or along transcutaneous catheter lines, is probably a more common means of entry. Regardless of the route of transcutaneous entry, the immaturity of the immune system, particularly opsonic mechanisms, then permits organisms of low pathogenic potential to mature hosts to establish disease in the preterm infant.¹²¹ The use of intravenous lipid supplements also favors the establishment of a nidus of infection once entry into the circulation has been obtained.¹¹³

CUTANEOUS BARRIER TO LIGHT INJURY

Energy absorbed from ultraviolet (UV) light passing through the skin may damage critical cellular functions through the generation of free radicals, principally singlet oxygen, as well as through inflammatory responses initiated by cytokine release and the generation of eicosanoids.

For example, free radical damage to deoxyribonucleic acid (DNA) may either result in cell death or initiate carcinogenic mutations. Although shorter wavelengths are more energetic and hence more damaging, they do not penetrate as deeply. In mature skin, ultraviolet B (UVB) (290–320 nm) does not penetrate into the dermis, but ultraviolet A (UVA) (320–400 nm) does, and visible wavelengths (400–800 nm) reach even deeper levels.¹²² Hence, in considering the effects of light on the skin, one must consider not only the cumulative energy of the light absorbed but also the depth of penetration. Cutaneous defenses against UV light injury include:

- Mechanisms that absorb or reflect light (e.g., stratum corneum, melanin)
- Enzymatic (e.g., superoxide dismutase, catalase, glutathione peroxidase) and nonenzymatic (e.g., ascorbate, β -carotene) systems that absorb singlet oxygen or interrupt free radical cascades initiated by superoxide and hydroxyl radicals
- Mechanisms to repair cellular and DNA damage.

Rules about depth of penetration of different wavelengths based on studies of mature skin may not hold for premature skin. For example, the stratum corneum is the first-line of defense, filtering out approximately 80% of incident UVB light.¹²² Therefore, the much thinner stratum corneum of the premature infant is one factor that would likely result in increased vulnerability to UV penetration. In addition, although melanocytes are present in the basal epidermis by the end of the first trimester, melanin granule formation is not fully mature, even at term (Table 4.1).¹⁰² Thus, inherent skin color is lighter in neonates. Moreover, the ability of melanocytes in the skin of preterm infants to increase melanin synthesis in response to UV stress is unknown. Other antioxidant defenses may be immature in the epidermis as they are in the lungs of preterm infants.¹²³ Taken together, it is apparent that the premature infant is particularly vulnerable to UV injury.

UVB is filtered out by window glass, but UVA is not. Thus, the preterm infant in the nursery may be exposed to solar UVA, as well as longer wavelengths from artificial light sources. UVA is implicated in certain phototoxic and photoallergic responses.¹²⁴ Chronic UVA exposure is linked to photoaging and is potentially carcinogenic.¹²⁵ Additionally, visible light in the near infrared range (760 nm – 1 mm) is now recognized to contribute to skin photoaging.¹²⁶

Portions of the visible light spectrum (420–500 nm) induce isomerization of bilirubin to compounds that can be excreted without hepatic conjugation. Hence, phototherapy with a variety of light sources is standard therapy for neonatal unconjugated hyperbilirubinemia. Because the commonly used fluorescent daylight bulbs emit UVA, the interposition of a Plexiglas® shield is essential to avoid burns in preterm infants.¹²⁷ Although long considered without risk of long-term complications, recent evidence points to increased numbers of melanocytic nevi (an important independent phenotypic risk factor for melanoma) in children who were exposed to neonatal phototherapy.^{128,129} However, several retrospective studies have not found an association with neonatal phototherapy in patients with non-melanoma skin cancer and melanoma, although these studies may not have sufficient follow-up time to capture this association, nor were these sequelae specifically studied in preterm infants. Severe phototoxicity is reported in a preterm infant following use of intravenous fluorescein with prolonged dye

retention due to renal immaturity.¹³⁰ Moreover, even internal organs are potentially affected by phototherapy, because light may penetrate more deeply through the skin of the preterm infant. For example, phototherapy has been linked to an increased incidence of symptomatic PDA in preterm infants.^{131,132} One study found that shielding the chest wall overlying the heart can mitigate this complication, suggesting a direct photoeffect on ductal tissue; however a follow-up study did not confirm this finding.^{132,133}

In summary, it should be assumed that the cutaneous barrier to the penetration of light is immature in the preterm infant, hence preterm infants should be physically shielded from exposure to sunlight from exterior windows and other sources of ultraviolet light. Limitation on the intensity of ambient nursery lighting is also recommended out of concern for a contribution to the retinopathy of prematurity.¹³⁴ It would seem prudent also to consider the potential deleterious cutaneous and transcutaneous effects of nursery lighting.

CUTANEOUS CONTRIBUTION TO IMMATURETY OF THERMAL HOMEOSTASIS

Body heat may escape through a number of mechanisms, as listed below:

- Evaporative heat loss (0.58 kcal/mL of evaporated water)
- Conduction: direct gain or loss of heat to objects in direct contact with the infant's body
- Convection: loss of body heat to the atmosphere, a function both of ambient air temperature and airflow (increased heat transfer with increased flow)
- Radiation (i.e. infrared energy exchanged between objects not in contact that absorb and remit radiant energy).

Maintenance of a thermally neutral environment, minimizing unwanted heat loss or heat gain, is a major challenge to those who care for premature infants. The survival of very low birthweight infants has been shown to be affected by alterations in thermoregulation, particularly in the 'golden-hour' immediately after birth.¹³⁵ The evaporation of amniotic fluid from the skin surface following birth constitutes a major thermal stressor to these infants. Interventions such as plastic wraps or bags, skin-to-skin care and transwarmer mattresses used immediately after delivery keep preterm infants warmer, leading to higher temperatures on admission to neonatal units and less hypothermia.⁴²

The skin participates in thermal homeostasis through several mechanisms. Water loss occurs both through passage of water across the stratum corneum as a function of barrier competency (see above) and from secreted water delivered to the skin surface by ducts (eccrine sweating) in response to neural and other stimuli.²³ Caloric losses caused by an immature skin barrier are a major contributor to the preterm infant's heat loss, particularly in the first week of life.^{135,136}

Conversely, because eccrine function is immature, the premature infant is unable to compensate for heat stress by sweating.¹³⁷ Even in term infants, sweating is not functionally mature because the term infant's set-point is higher than in mature individuals. Sweating in preterm infants matures rapidly following birth; however, the efficiency remains poor, with fewer body sites sweating in response to thermal stimuli and maintenance of a high set-point.¹³⁷ Vasomotor control of cutaneous blood flow is a third component of the skin's contribution to

thermal homeostasis. Both vasoconstriction and vasodilation in response to thermal stimuli are attenuated in the skin of preterm infants, although these responses appear to mature within 2–3 weeks.^{23,138} Finally, the subcutaneous adipose reservoir is deficient in preterm infants, reducing both their insulation against heat loss and their energy reserves for thermal conversion.

NEUROCUTANEOUS DEVELOPMENT IN THE PREMATURE INFANT

Responsiveness to touch is present at a very early age: that is, by the end of the first trimester, the fetus withdraws in response to skin stroking.¹³⁹ In the preterm infant, neurocutaneous responses may be immature and ‘globalized’. Thus, in the unstable premature infant, handling is minimized to avoid adverse effects of skin stimulation, such as changes in heart rate, hypoxia, and apneic episodes.^{140,141} However, older and more stable preterm infants may benefit from skin contact in the form of skin-to-skin contact and massage.¹⁴²

Originally, skin-to-skin contact was explored as a mechanism to facilitate maternal bonding with the term infant. A modification of this principle, designated ‘kangaroo care,’ has been advocated for preterm infants in developing countries as a safe and effective mode of care for stable premature infants^{143,144} in which the infant is continually housed against the mother’s skin and permitted *ad libitum* breast-feeding. In low-income countries, kangaroo care can reduce both morbidity and mortality from inadequate thermal protection and infections associated with overcrowding in nurseries and formula-feedings.¹⁴³ Briefer periods of maternal skin-to-skin contact have also been advocated in the care of the preterm infant in high-income countries as a means to enhance maternal confidence and to humanize the nursery experience.^{143–146} When preterm infants as early as 22 weeks’ gestational age are carefully selected to avoid the inclusion of unstable ones, the practice does not appear to be deleterious, and may be beneficial (e.g., reduce periods of ‘purposeless’ activity).^{147,148} Recent studies suggest that autonomic and psychomotor pain responses are improved in preterm infants who have skin-to-skin contact during heel-sticks, compared with those receiving conventional incubator care.^{149,150} Long-term benefits to mother and child of skin-to-skin contact are difficult to distinguish from the benefits of more conventional mother–child contact, but may include prolonged maternal lactation and less infant crying.¹⁴³

Infant massage has been advocated by some as a way to decrease stress and promote growth and development of preterm infants. The mechanisms by which massage improves weight gain are not completely understood, but may involve increased vagal tone, which leads to increased gastric motility, and levels of insulin and insulin-like growth factor-1.¹⁵¹ If larger studies confirm its utility, this relatively simple intervention has the potential to significantly improve weight gain and developmental outcomes, thus decreasing length of hospital stay.¹⁵²

Although it may seem intuitively obvious that both parents and infants would benefit psychologically from the humanizing effects of skin-to-skin contact, the neurocutaneous pathways that are likely to underlie these responses are only beginning to be delineated in mature skin.¹⁵³ It will be important, as this work proceeds, to examine the maturation of these pathways in the preterm infant, so as to both better understand the

capacity of the maturing infant to respond to these external stimuli and to develop systems of care that are both rational and ‘humanistic’.

Skin diseases in the premature infant

BARRIER FUNCTION OF ABNORMAL SKIN

The consequences of barrier immaturity in premature infants may be compounded if the infant also has a primary skin disorder. Infants with severe genetic skin disorders are often born prematurely. Skin diseases that result in hyperkeratosis (scaling) or a thickened stratum corneum, such as the ichthyoses, are commonly associated with impaired barrier function.¹⁵⁴ These infants are at-risk for hypernatremia as a result of increased evaporative loss of free water from the skin surface (see [Chapter 19](#)).^{155,156} Similarly, infants with widespread blistering diseases, whether resulting from underlying infection, as in staphylococcal scalded skin syndrome, or from one of the genetic mechanobullous diseases, e.g., epidermolysis bullosa, have increased fluid requirements as a result of loss of barrier integrity. Skin disease also increases the risk of systemic absorption of topical medications, both because of a further compromise in barrier competence and because of increased exposure to topical medications. Instances of this include prolonged use of topical steroids to dermatitic skin, resulting in adrenal suppression and other signs of hypercortisolism,^{157,158} and use of salicylate-containing ointments to remove excessive scale, resulting in salicylism.¹⁵⁹ Skin diseases can also increase the risk of systemic infection by providing portals of entry through breaks in skin integrity.

SCARS OF PREMATURITY

A number of nursery procedures may lead to scars; the number of scars nursery graduates bear is correlated with their degree of prematurity and the duration of intensive care (see also [Chapter 8](#)).¹⁶⁰ Although most of these scars are not of great concern, more severe scarring sequelae can occur, particularly those resulting from wounds from chest tubes, skin stripping from adhesive tapes, and extravasated intravenous fluids. In addition, very premature infants (<29 weeks) may develop atrophic scars or so-called ‘anetoderma of prematurity’.¹⁶¹ Although the term ‘anetoderma’ implies a loss of elastic tissue and clinically manifests as an ‘outpouching’ of the skin, scars of prematurity can also be flat. These scars often only become evident at a few weeks to months of life. They often develop at sites of previous application of monitors and adhesives, but may also develop in areas that do not correspond to known areas of injury ([Fig. 4.3](#)).

HEMANGIOMAS

Infantile hemangiomas are more common in preterm infants and their frequency is related to the degree of prematurity.¹⁶² In contrast to term infants, there is no significant female predominance in preterm infants with hemangiomas. Premature infants also have higher risk of having multiple hemangiomas, but the exact basis for this increase is not known.¹⁶² Hypotheses include the possibility that preterm infants have higher numbers of endothelial progenitor cells than term infants, and/or are



Figure 4.3 Scars of prematurity. (A). Former 25-week gestational age infant with scars on the abdomen. Such scarring is not rare in very premature infants but may not be noted until several months of age. (B). Subtle, horizontal, linear scars on the leg of a former 27-week gestational age twin which were likely caused by tape used to hold an IV in place. The scars were not noted until several months of age. (A: Courtesy of Linda Beets-Shay, MD.)

more frequently exposed to medications that may predispose them to hemangiomas such as beta-2-sympathomimetic medications for tocolysis in preterm labor, or erythropoietin (see Chapter 21).^{162–165}

Summary

Neonatologists have long been cognizant of the importance of fluid balance and thermal homeostasis in the care of the premature infant. Now, through advances in the care of fragile premature infants, and particularly through the advent of surfactant replacement therapy, neonates of ever-greater prematurity survive, relentlessly pushing back the age of viability. In this context, the consequences of skin barrier immaturity have emerged as a critical frontier in their management. Barrier failure contributes to the morbidity and mortality of the preterm neonate through fluid and electrolyte instability and the effects of fluid imbalance on blood volume and blood pressure, as well as an increased susceptibility to transcutaneous infections and toxicity from transcutaneous absorption of xenobiotics. As a result of the interlocking interdependence of organ systems, all of which are immature, the magnitude of the skin's contribution to neonatal morbidity cannot currently be estimated.

At present, it is only possible to outline broad principles for the care of the premature infant's skin. Most of these are

self-evident, such as the need to avoid exposure to topical agents of potential systemic toxicity, or for gentle handling to prevent abrogation of the skin's integrity. However, the optimal application of these principles in practice is often less evident. For example, all ingredients in topical medicaments, emollients, or cleansers need to be identified and their potential for toxicity considered, yet this information may not be easily obtained.⁴³ In most instances, skin care practices have not been systematically studied to determine optimal regimens. Just as the term infant's skin is more resilient and protective than the skin of a premature infant of 30 weeks' gestation, procedures that may not be hazardous to an infant of this gestational age may be toxic to the extremely immature 'micropreemie.' Therefore, in designing future studies, it will be important to consider the differences in skin function in babies of varying gestational and postnatal ages. Greater awareness of skin functions and their physiologic bases, as well as the infant's position on the maturational timetable of these functions, will be needed for the development of rational regimens of skin care in the future.

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KEY REFERENCES

23. Fluhr JW, Darlenski R, Taieb A, et al. Functional skin adaptation in infancy – almost complete but not fully competent. *Exp Dermatol* 2010;19(6):483–92.
25. Visscher MO, Taylor T, Narendran V. Neonatal intensive care practices and the influence on skin condition. *J Eur Acad Dermatol Venereol* 2013;27(4):486–93.
34. Williams PR, Oh W. Effects of radiant warmer on insensible water loss in newborn infants. *Am J Dis Child* 1974;128(4):511–14.
41. Kaushal M, Agarwal R, Aggarwal R, et al. Cling wrap, an innovative intervention for temperature maintenance and reduction of insensible water loss in very low-birthweight babies nursed under radiant warmers: a randomized, controlled trial. *Ann Trop Paediatr* 2005;25(2): 111–18.
54. Cockayne SE, Lee JA, Harrington CI. Oleo-granulomatous response in lymph nodes associated with emollient use in Netherton's syndrome. *Br J Dermatol* 1999;141(3):562–4.
62. Visscher MO, Barai N, LaRuffa AA, et al. Epidermal barrier treatments based on vernix

- caseosa. *Skin Pharmacol Physiol* 2011;24(6):322–9.
128. Csoma Z, Hencz P, Orvos H, et al. Neonatal blue-light phototherapy could increase the risk of dysplastic nevus development. *Pediatrics* 2007;119(5):1036–7; author reply 1037–8.
147. Karlsson V, Heinemann AB, Sjors G, et al. Early skin-to-skin care in extremely preterm infants: thermal balance and care environment. *J Pediatr* 2012;161(3):422–6.
151. Field T, Diego M, Hernandez-Reif M. Preterm infant massage therapy research: a review. *Infant Behav Dev* 2010;33(2):115–24.
161. Prizant TL, Lucky AW, Frieden IJ, et al. Spontaneous atrophic patches in extremely premature infants. *Anetoderma of prematurity*. *Arch Dermatol* 1996;132(6):671–4.

REFERENCES

- Elias PM, Menon GK. Structural and lipid biochemical correlates of the epidermal permeability barrier. *Adv Lipid Res* 1991;24:1–26.
- Evans NJ, Rutter N. Development of the epidermis in the newborn. *Biol Neonate* 1986; 49(2):74–80.
- Visscher MO, Narendran V, Pickens WL, et al. Vernix caseosa in neonatal adaptation. *J Perinatol* 2005;25(7):440–6.
- Ballard JL, Khoury JC, Wedig K, et al. New Ballard Score, expanded to include extremely premature infants. *J Pediatr* 1991;119(3): 417–23.
- Hammarlund K, Sedin G. Transepidermal water loss in newborn infants. III. Relation to gestational age. *Acta Paediatr Scand* 1979;68(6):795–801.
- Harpin VA, Rutter N. Barrier properties of the newborn infant's skin. *J Pediatr* 1983;102(3): 419–25.
- Nachman RL, Esterly NB. Increased skin permeability in preterm infants. *J Pediatr* 1971; 79(4):628–32.
- Okah FA, Wickett RR, Pickens WL, et al. Surface electrical capacitance as a noninvasive bedside measure of epidermal barrier maturation in the newborn infant. *Pediatrics* 1995; 96(4 Pt 1):688–92.
- Emery MM, Hebert AA, Aguirre Vila-Coro A, et al. The relationship between skin maturation and electrical skin impedance. *J Dermatol Sci* 1991;2(5):336–40.
- Aszterbaum M, Menon GK, Feingold KR, et al. Ontogeny of the epidermal barrier to water loss in the rat: correlation of function with stratum corneum structure and lipid content. *Pediatr Res* 1992;31(4 Pt 1):308–17.
- Williams ML, Hanley K, Elias PM, et al. Ontogeny of the epidermal permeability barrier. *J Invest Dermatol Symp Proc* 1998;3(2):75–9.
- Kalia YN, Nonato LB, Lund CH, et al. Development of skin barrier function in premature infants. *J Invest Dermatol* 1998;111(2):320–6.
- Agren J, Sjors G, Sedin G. Transepidermal water loss in infants born at 24 and 25 weeks of gestation. *Acta Paediatr* 1998;87(11): 1185–90.
- Hanley K, Jiang Y, Elias PM, et al. Acceleration of barrier ontogenesis in vitro through air exposure. *Pediatr Res* 1997;41(2):293–9.
- Williams ML, Feingold KR. Barrier function of neonatal skin. *J Pediatr* 1998;133(3):467–8.
- Agren J, Sjors G, Sedin G. Ambient humidity influences the rate of skin barrier maturation in extremely preterm infants. *J Pediatr* 2006; 148(5):613–17.
- Hammarlund K, Sedin G. Transepidermal water loss in newborn infants. IV. Small for gestational age infants. *Acta Paediatr Scand* 1980;69(3):377–83.
- Aszterbaum M, Feingold KR, Menon GK, et al. Glucocorticoids accelerate fetal maturation of the epidermal permeability barrier in the rat. *J Clin Invest* 1993;91(6):2703–8.
- Effect of corticosteroids for fetal maturation on perinatal outcomes. NIH Consensus Development Panel on the Effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA* 1995;273(5):413–18.
- Omar SA, DeCristofaro JD, Agarwal BI, et al. Effects of prenatal steroids on water and sodium homeostasis in extremely low birth weight neonates. *Pediatrics* 1999;104(3 Pt 1): 482–8.
- Jain A, Rutter N, Cartledge PH. Influence of antenatal steroids and sex on maturation of the epidermal barrier in the preterm infant. *Arch Dis Child Fetal Neonatal Ed* 2000;83(2): F112–16.
- Fluhr JW, Crumrine D, Mao-Qiang M, et al. Topical liver x receptor activators accelerate postnatal acidification of stratum corneum and improve function in the neonate. *J Invest Dermatol* 2005;125(6):1206–14.
- Fluhr JW, Darlenski R, Taieb A, et al. Functional skin adaptation in infancy – almost complete but not fully competent. *Exp Dermatol* 2010;19(6):483–92.
- Visscher M, Odio M, Taylor T, et al. Skin care in the NICU patient: effects of wipes versus cloth and water on stratum corneum integrity. *Neonatology* 2009;96(4):226–34.
- Visscher MO, Taylor T, Narendran V. Neonatal intensive care practices and the influence on skin condition. *J Eur Acad Dermatol Venereol* 2013;27(4):486–93.
- Cartledge PH, Rutter N. Skin barrier function. In: Polin RA, Fox WW, editors. *Fetal and neonatal physiology*. 2nd ed. Philadelphia: WB Saunders; 1998. p. 771.
- Wu PY, Hodgman JE. Insensible water loss in preterm infants: changes with postnatal development and non-ionizing radiant energy. *Pediatrics* 1974;54(6):704–12.
- Fanaroff AA, Wald M, Gruber HS, et al. Insensible water loss in low birth weight infants. *Pediatrics* 1972;50(2):236–45.
- Hammarlund K, Nilsson GE, Oberg PA, et al. Transepidermal water loss in newborn infants. I. Relation to ambient humidity and site of measurement and estimation of total transepidermal water loss. *Acta Paediatr Scand* 1977; 66:553–62.
- Maayan-Metzger A, Yosipovitch G, Hadad E, et al. Transepidermal water loss and skin hydration in preterm infants during phototherapy. *Am J Perinatol* 2001;18(7):393–6.
- Oh W, Karecki H. Phototherapy and insensible water loss in the newborn infant. *Am J Dis Child* 1972;124(2):230–2.
- Kjartansson S, Hammarlund K, Sedin G. Insensible water loss from the skin during phototherapy in term and preterm infants. *Acta Paediatr* 1992;81(10):764–8.
- Bertini G, Perugi S, Elia S, et al. Transepidermal water loss and cerebral hemodynamics in preterm infants: conventional versus LED phototherapy. *Eur J Pediatr* 2008;167(1): 37–42.
- Williams PR, Oh W. Effects of radiant warmer on insensible water loss in newborn infants. *Am J Dis Child* 1974;128(4):511–14.
- Kim SM, Lee EY, Chen J, et al. Improved care and growth outcomes by using hybrid humidified incubators in very preterm infants. *Pediatrics* 2010;125(1):e137–45.
- Kjartansson S, Arsan S, Hammarlund K, et al. Water loss from the skin of term and preterm infants nursed under a radiant heater. *Pediatr Res* 1995;37(2):233–8.
- Bell EF, Neidich GA, Cashore WJ, et al. Combined effect of radiant warmer and phototherapy on insensible water loss in low-birth-weight infants. *J Pediatr* 1979;94(5):810–13.
- Marks KH, Friedman Z, Maisels MJ. A simple device for reducing insensible water loss in low-birth-weight infants. *Pediatrics* 1977; 60(2):223–6.
- Cramer K, Wiebe N, Hartling L, et al. Heat loss prevention: a systematic review of occlusive skin wrap for premature neonates. *J Perinatol* 2005;25(12):763–9.
- Gurgel Ede P, Caetano JA, Lopes MV, et al. The effectiveness of using semipermeable membrane in preterm infants to reduce transepidermal losses. *Rev Esc Enferm USP* 2011; 45(4):818–24.
- Kaushal M, Agarwal R, Aggarwal R, et al. Cling wrap, an innovative intervention for temperature maintenance and reduction of insensible water loss in very low-birthweight babies nursed under radiant warmers: a randomized, controlled trial. *Ann Trop Paediatr* 2005;25(2): 111–18.
- McCall EM, Alderdice FA, Halliday HL, et al. Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. *Cochrane Database Syst Rev* 2008;(1): CD004210.
- Siegfried EC. Neonatal skin and skin care. *Dermatol Clin* 1998;16(3):437–46.
- Knauth A, Gordin M, McNelis W, et al. Semipermeable polyurethane membrane as an artificial skin for the premature neonate. *Pediatrics* 1989;83(6):945–50.
- Vernon HJ, Lane AT, Wischerath LJ, et al. Semipermeable dressing and transepidermal water loss in premature infants. *Pediatrics* 1990; 86(3):357–62.
- Donahue ML, Phelps DL, Richter SE, et al. A semipermeable skin dressing for extremely low birth weight infants. *J Perinatol* 1996;16(1): 20–6.
- Mancini AJ, Sookdeo-Drost S, Madison KC, et al. Semipermeable dressings improve epidermal barrier function in premature infants. *Pediatr Res* 1994;36(3):306–14.
- Katz S, McGinley K, Leyden JJ. Semipermeable occlusive dressings. Effects on growth of pathogenic bacteria and reepithelialization of superficial wounds. *Arch Dermatol* 1986; 122(1):58–62.
- Rutter N, Hull D. Reduction of skin water loss in the newborn. I. Effect of applying topical agents. *Arch Dis Child* 1981;56(9):669–72.
- Nopper AJ, Horii KA, Sookdeo-Drost S, et al. Topical ointment therapy benefits premature infants. *J Pediatr* 1996;128(5 Pt 1):660–9.
- Brandon DH, Coe K, Hudson-Barr D, et al. Effectiveness of No-Sting skin protectant and Aquaphor on water loss and skin integrity in premature infants. *J Perinatol* 2010;30(6): 414–19.
- Mao-Qiang M, Brown BE, Wu-Pong S, et al. Exogenous nonphysiologic vs physiologic lipids. Divergent mechanisms for correction of permeability barrier dysfunction. *Arch Dermatol* 1995;131(7):809–16.
- Lester DE. Normal paraffins in living matter – occurrence, metabolism and pathology. *Prog Food Nutr Sci* 1979;3(1–2):1–66.
- Cockayne SE, Lee JA, Harrington CI. Oleo-granulomatous response in lymph nodes associated with emollient use in Netherton's syndrome. *Br J Dermatol* 1999;141(3):562–4.
- Conner JM, Soll RF, Edwards WH. Topical ointment for preventing infection in preterm infants. *Cochrane Database Syst Rev* 2004;(1): CD001150.
- Darmstadt GL, Badrawi N, Law PA, et al. Topically applied sunflower seed oil prevents invasive bacterial infections in preterm infants in

- Egypt: a randomized, controlled clinical trial. *Pediatr Infect Dis J* 2004;23(8):719–25.
57. Darmstadt GL, Saha SK, Ahmed AS, et al. Effect of skin barrier therapy on neonatal mortality rates in preterm infants in Bangladesh: a randomized, controlled, clinical trial. *Pediatrics* 2008;121(3):522–9.
 58. Darmstadt GL, Saha SK, Ahmed AS, et al. Effect of topical treatment with skin barrier-enhancing emollients on nosocomial infections in preterm infants in Bangladesh: a randomised controlled trial. *Lancet* 2005;365(9464):1039–45.
 59. Man MQ, Feingold KR, Elias PM. Exogenous lipids influence permeability barrier recovery in acetone-treated murine skin. *Arch Dermatol* 1993;129(6):728–38.
 60. Zettersten EM, Ghadially R, Feingold KR, et al. Optimal ratios of topical stratum corneum lipids improve barrier recovery in chronologically aged skin. *J Am Acad Dermatol* 1997;37(3 Pt 1):403–8.
 61. Sugarman JL, Parish LC. Efficacy of a lipid-based barrier repair formulation in moderate-to-severe pediatric atopic dermatitis. *J Drugs Dermatol* 2009;8(12):1106–11.
 62. Visscher MO, Barai N, LaRuffa AA, et al. Epidermal barrier treatments based on vernix caseosa. *Skin Pharmacol Physiol* 2011;24(6):322–9.
 63. West DP, Halket JM, Harvey DR, et al. Percutaneous absorption in preterm infants. *Pediatr Dermatol* 1987;4(3):234–7.
 64. Rutter N. Percutaneous drug absorption in the newborn: hazards and uses. *Clin Perinatol* 1987;14(4):911–30.
 65. Scheuplein RJ, Blank IH. Permeability of the skin. *Physiol Rev* 1971;51(4):702–47.
 66. West DP, Worobec S, Solomon LM. Pharmacology and toxicology of infant skin. *J Invest Dermatol* 1981;76(3):147–50.
 67. Menon GK, Elias PM. Morphologic basis for a pore-pathway in mammalian stratum corneum. *Skin Pharmacol* 1997;10(5–6):235–46.
 68. Froman RD, Owen SV, Murphy C. Isopropyl pad use in neonatal intensive care units. *J Perinatol* 1998;18(3):216–20.
 69. Linder N, Davidovitch N, Reichman B, et al. Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *J Pediatr* 1997;131(3):434–9.
 70. Lashkari HP, Chow P, Godambe S. Aqueous 2% chlorhexidine-induced chemical burns in an extremely premature infant. *Arch Dis Child Fetal Neonatal Ed* 2012;97(1):F64.
 71. Bringue Espuny X, Soria X, Sole E, et al. Chlorhexidine-methanol burns in two extreme preterm newborns. *Pediatr Dermatol* 2010;27(6):676–8.
 72. Mannan K, Chow P, Lissauer T, et al. Mistaken identity of skin cleansing solution leading to extensive chemical burns in an extremely preterm infant. *Acta Paediatr* 2007;96(10):1536–7.
 73. Harpin V, Rutter N. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1982;57(6):477–9.
 74. Reynolds PR, Banerjee S, Meek JH. Alcohol burns in extremely low birthweight infants: still occurring. *Arch Dis Child Fetal Neonatal Ed* 2005;90(1):F10.
 75. Rogers SC, Burrows D, Neill D. Percutaneous absorption of phenol and methyl alcohol in Magenta Paint B.P.C. *Br J Dermatol* 1978;98(5):559–60.
 76. American Academy of Pediatrics. Committee on Drugs. Camphor: Who needs it? *Pediatrics* 1978;62(3):404–6.
 77. Benda GI, Hiller JL, Reynolds JW. Benzyl alcohol toxicity: impact on neurologic handicaps among surviving very low birth weight infants. *Pediatrics* 1986;77(4):507–12.
 78. Bamford MF, Jones LF. Deafness and biochemical imbalance after burns treatment with topical antibiotics in young children. Report of 6 cases. *Arch Dis Child* 1978;53(4):326–9.
 79. Stohs SJ, Ezzedeen FW, Anderson AK, et al. Percutaneous absorption of iodochlorhydroxyquin in humans. *J Invest Dermatol* 1984;82(2):195–8.
 80. MacDonald MG, Getson PR, Glasgow AM, et al. Propylene glycol: increased incidence of seizures in low birth weight infants. *Pediatrics* 1987;79(4):622–5.
 81. Bishop NJ, Morley R, Day JP, et al. Aluminum neurotoxicity in preterm infants receiving intravenous-feeding solutions. *N Engl J Med* 1997;336(22):1557–61.
 82. Barker N, Hadgraft J, Rutter N. Skin permeability in the newborn. *J Invest Dermatol* 1987;88(4):409–11.
 83. Armstrong RW, Eichner ER, Klein DE, et al. Pentachlorophenol poisoning in a nursery for newborn infants. II. Epidemiologic and toxicologic studies. *J Pediatr* 1969;75(2):317–25.
 84. Pramanik AK, Hansen RC. Transcutaneous gamma benzene hexachloride absorption and toxicity in infants and children. *Arch Dermatol* 1979;115(10):1224–5.
 85. l'Allemand D, Gruters A, Beyer P, et al. Iodine in contrast agents and skin disinfectants is the major cause for hypothyroidism in premature infants during intensive care. *Horm Res* 1987;28(1):42–9.
 86. Parravicini E, Fontana C, Paterlini GL, et al. Iodine, thyroid function, and very low birth weight infants. *Pediatrics* 1996;98(4 Pt 1):730–4.
 87. Bhandarkar SS, MacKelfresh J, Fried L, et al. Targeted therapy of oral hairy leukoplakia with gentian violet. *J Am Acad Dermatol* 2008;58(4):711–12.
 88. Barrett DA, Rutter N. Transdermal delivery and the premature neonate. *Crit Rev Ther Drug Carrier Syst* 1994;11(1):1–30.
 89. Smerdely P, Lim A, Boyages SC, et al. Topical iodine-containing antiseptics and neonatal hypothyroidism in very-low-birthweight infants. *Lancet* 1989;2(8664):661–4.
 90. Upadhyayula S, Kambalappalli M, Harrison CJ. Safety of anti-infective agents for skin preparation in premature infants. *Arch Dis Child* 2007;92(7):646–7.
 91. Hibbard JS, Mulberry GK, Brady AR. A clinical study comparing the skin antiseptics and safety of ChlorPrep, 70% isopropyl alcohol, and 2% aqueous chlorhexidine. *J Infus Nurs* 2002;25(4):244–9.
 92. Bell EF, Warburton D, Stonestreet BS, et al. Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. *N Engl J Med* 1980;302(11):598–604.
 93. McCrea HJ, Ment LR. The diagnosis, management, and postnatal prevention of intraventricular hemorrhage in the preterm neonate. *Clin Perinatol* 2008;35(4):777–92, vii.
 94. Bauer K, Versmold H. Postnatal weight loss in preterm neonates less than 1,500 g is due to isotonic dehydration of the extracellular volume. *Acta Paediatr Scand Suppl* 1989;360:37–42.
 95. Oh W, Poindexter BB, Perritt R, et al. Association between fluid intake and weight loss during the first ten days of life and risk of bronchopulmonary dysplasia in extremely low birth weight infants. *J Pediatr* 2005;147(6):786–90.
 96. Musemeche CA, Kosloske AM, Bartow SA, et al. Comparative effects of ischemia, bacteria, and substrate on the pathogenesis of intestinal necrosis. *J Pediatr Surg* 1986;21(6):536–8.
 97. Willoughby RE Jr, Pickering LK. Necrotizing enterocolitis and infection. *Clin Perinatol* 1994;21(2):307–15.
 98. Bell EF, Warburton D, Stonestreet BS, et al. High-volume fluid intake predisposes premature infants to necrotizing enterocolitis. *Lancet* 1979;2(8133):90.
 99. Nowicki PT, Nankervis CA. The role of the circulation in the pathogenesis of necrotizing enterocolitis. *Clin Perinatol* 1994;21(2):219–34.
 100. Crissinger KD, Granger DN. Mucosal injury induced by ischemia and reperfusion in the piglet intestine: influences of age and feeding. *Gastroenterology* 1989;97(4):920–6.
 101. Williams ML, Le K. The permeability barrier in the preterm infant: Review of the clinical consequences of barrier immaturity and of insights derived from an animal model of barrier ontogenesis, with a call for future studies. *Eur J Pediatr Dermatol* 1998;8(8):101–6.
 102. Morasso MI, Chu DH, Schwartz T. Structure and function of the skin. In: Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 4th ed. Philadelphia: Elsevier; 2011. p. 1.
 103. Rimdeika R, Bagdonas R. Major full thickness skin burn injuries in premature neonate twins. *Burns* 2005;31(1):76–84.
 104. Lund CH, Nonato LB, Kuller JM, et al. Disruption of barrier function in neonatal skin associated with adhesive removal. *J Pediatr* 1997;131(3):367–72.
 105. Dollison EJ, Beckstrand J. Adhesive tape vs pectin-based barrier use in preterm infants. *Neonatal Netw* 1995;14(4):35–9.
 106. Denyer J. Reducing pain during the removal of adhesive and adherent products. *Br J Nurs* 2011;20(15):S28, S30–5.
 107. Miller SJ, Aly R, Shinefeld HR, et al. In vitro and in vivo antistaphylococcal activity of human stratum corneum lipids. *Arch Dermatol* 1988;124(2):209–15.
 108. Bibel DJ, Aly R, Shinefield HR. Topical sphingolipids in antiseptics and antifungal therapy. *Clin Exp Dermatol* 1995;20(5):395–400.
 109. Braff MH, Bardan A, Nizet V, et al. Cutaneous defense mechanisms by antimicrobial peptides. *J Invest Dermatol* 2005;125(1):9–13.
 110. Marchini G, Lindow S, Brismar H, et al. The newborn infant is protected by an innate antimicrobial barrier: peptide antibiotics are present in the skin and vernix caseosa. *Br J Dermatol* 2002;147(6):1127–34.
 111. Eastick K, Leeming JP, Bennett D, et al. Reservoirs of coagulase negative staphylococci in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1996;74(2):F99–104.
 112. Freeman J, Epstein MF, Smith NE, et al. Extra hospital stay and antibiotic usage with nosocomial coagulase-negative staphylococcal bacteremia in two neonatal intensive care unit populations. *Am J Dis Child* 1990;144(3):324–9.

113. Freeman J, Goldmann DA, Smith NE, et al. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *N Engl J Med* 1990;323(5):301–8.
114. Klein JO. From harmless commensal to invasive pathogen – coagulase-negative staphylococci. *N Engl J Med* 1990;323(5):339–40.
115. Nataro JP, Corcoran L, Zirin S, et al. Prospective analysis of coagulase-negative staphylococcal infection in hospitalized infants. *J Pediatr* 1994;125(5 Pt 1):798–804.
116. Stuart SM, Lane AT. *Candida* and *Malassezia* as nursery pathogens. *Semin Dermatol* 1992; 11(1):19–23.
117. Chang HJ, Miller HL, Watkins N, et al. An epidemic of *Malassezia* pachydermatis in an intensive care nursery associated with colonization of health care workers' pet dogs. *N Engl J Med* 1998;338(11):706–11.
118. Rowen JL, Correa AG, Sokol DM, et al. Invasive aspergillosis in neonates: report of five cases and literature review. *Pediatr Infect Dis J* 1992;11(7):576–82.
119. Linder N, Keller N, Huri C, et al. Primary cutaneous mucormycosis in a premature infant: case report and review of the literature. *Am J Perinatol* 1998;15(1):35–8.
120. Rowen JL, Atkins JT, Levy ML, et al. Invasive fungal dermatitis in the < or = 1000-gram neonate. *Pediatrics* 1995;95(5):682–7.
121. Zilow EP, Hauck W, Linderkamp O, et al. Alternative pathway activation of the complement system in preterm infants with early onset infection. *Pediatr Res* 1997;41(3):334–9.
122. Kochevar I, Taylor C, Krutmann J. Fundamentals of cutaneous photobiology and photoimmunology: Introduction. In: Goldsmith L, Katz S, Gilchrist B, et al, editors. *Fitzpatrick's dermatology in general medicine*. 8th ed. New York: McGraw-Hill; 2012. p. 1031.
123. Frank L, Sosenko IR. Development of lung antioxidant enzyme system in late gestation: possible implications for the prematurely born infant. *J Pediatr* 1987;110(1):9–14.
124. Vandergriff T, Bergstresser P. Abnormal responses to ultraviolet radiation: idiopathic, probably immunologic, and photoexacerbated. In: Goldsmith L, Katz S, Gilchrist B, et al, editors. *Fitzpatrick's dermatology in general medicine*. 8th ed. New York: McGraw-Hill; 2012. p. 1049.
125. Halliday GM, Byrne SN, Damian DL. Ultraviolet A radiation: its role in immunosuppression and carcinogenesis. *Semin Cutan Med Surg* 2011;30(4):214–21.
126. Schroeder P, Haendeler J, Krutmann J. The role of near infrared radiation in photoaging of the skin. *Exp Gerontol* 2008;43(7):629–32.
127. Siegfried EC, Stone MS, Madison KC. Ultraviolet light burn: a cutaneous complication of visible light phototherapy of neonatal jaundice. *Pediatr Dermatol* 1992;9(3): 278–82.
128. Csoma Z, Hencz P, Orvos H, et al. Neonatal blue-light phototherapy could increase the risk of dysplastic nevus development. *Pediatrics* 2007;119(5):1036–7; author reply 1037–8.
129. Matichard E, Le Henaff A, Sanders A, et al. Effect of neonatal phototherapy on melanocytic nevus count in children. *Arch Dermatol* 2006;142(12):1599–604.
130. Kearns GL, Williams BJ, Timmons OD. Fluorescein phototoxicity in a premature infant. *J Pediatr* 1985;107(5):796–8.
131. Barefield ES, Dwyer MD, Cassady G. Association of patent ductus arteriosus and phototherapy in infants weighing less than 1000 grams. *J Perinatol* 1993;13(5):376–80.
132. Rosenfeld W, Sadhev S, Brunot V, et al. Phototherapy effect on the incidence of patent ductus arteriosus in premature infants: prevention with chest shielding. *Pediatrics* 1986;78(1):10–14.
133. Travadi J, Simmer K, Ramsay J, et al. Patent ductus arteriosus in extremely preterm infants receiving phototherapy: does shielding the chest make a difference? A randomized, controlled trial. *Acta Paediatr* 2006;95(11): 1418–23.
134. Glass P, Avery GB, Subramanian KN, et al. Effect of bright light in the hospital nursery on the incidence of retinopathy of prematurity. *N Engl J Med* 1985;313(7):401–4.
135. Bissinger RL, Annibale DJ. Thermoregulation in very low-birth-weight infants during the golden hour: results and implications. *Adv Neonatal Care* 2010;10(5):230–8.
136. Hammarlund K, Stromberg B, Sedin G. Heat loss from the skin of preterm and fullterm newborn infants during the first weeks after birth. *Biol Neonate* 1986;50(1):1–10.
137. Harpin VA, Rutter N. Sweating in preterm babies. *J Pediatr* 1982;100(4):614–19.
138. Jahnukainen T, van Ravenswaaij-Arts C, Jalonen J, et al. Dynamics of vasomotor thermoregulation of the skin in term and preterm neonates. *Early Hum Dev* 1993;33(2): 133–43.
139. Hogg ID. Sensory nerves and associated structures in the skin of human fetuses of 8 to 14 weeks of menstrual age correlate with functional capability. *J Comp Neurol* 1941;75:371.
140. Long JG, Philip AG, Lucey JF. Excessive handling as a cause of hypoxemia. *Pediatrics* 1980;65(2):203–7.
141. Lynch ME. Iatrogenic hazards, adverse occurrences, and complications involving NICU nursing practice. *J Perinat Neonatal Nurs* 1991;5(3):78–86.
142. Field TM, Schanberg SM, Scafidi F, et al. Tactile/kinesthetic stimulation effects on preterm neonates. *Pediatrics* 1986;77(5): 654–8.
143. Cattaneo A, Davanzo R, Uxa F, et al. Recommendations for the implementation of Kangaroo Mother Care for low birthweight infants. *International Network on Kangaroo Mother Care. Acta Paediatr* 1998;87(4):440–5.
144. Tessier R, Cristo M, Velez S, et al. Kangaroo mother care and the bonding hypothesis. *Pediatrics* 1998;102(2):e17.
145. Whitelaw A, Heisterkamp G, Sleath K, et al. Skin to skin contact for very low birthweight infants and their mothers. *Arch Dis Child* 1988;63(11):1377–81.
146. Ludington-Hoe SM, Thompson C, Swinth J, et al. Kangaroo care: research results, and practice implications and guidelines. *Neonatal Netw* 1994;13(1):19–27.
147. Karlsson V, Heinemann AB, Sjors G, et al. Early skin-to-skin care in extremely preterm infants: thermal balance and care environment. *J Pediatr* 2012;161(3):422–6.
148. Abouelfetoh A, Ludington-Hoe SM, Burant CJ, et al. Effect of skin-to-skin contact on preterm infant skin barrier function and hospital-acquired infection. *J Clin Med Res* 2011;3(1):36–46.
149. Cong X, Cusson RM, Walsh S, et al. Effects of skin-to-skin contact on autonomic pain responses in preterm infants. *J Pain* 2012; 13(7):636–45.
150. Castral TC, Warnock F, Leite AM, et al. The effects of skin-to-skin contact during acute pain in preterm newborns. *Eur J Pain* 2008; 12(4):464–71.
151. Field T, Diego M, Hernandez-Reif M. Preterm infant massage therapy research: a review. *Infant Behav Dev* 2010;33(2):115–24.
152. Vickers A, Ohlsson A, Lacy JB, et al. Massage for promoting growth and development of preterm and/or low birth-weight infants. *Cochrane Database Syst Rev* 2004;(2): CD000390.
153. O'Sullivan RL, Lipper G, Lerner EA. The neuro-immuno-cutaneous-endocrine network: relationship of mind and skin. *Arch Dermatol* 1998;134(11):1431–5.
154. Buyse L, Graves C, Marks R, et al. Collodion baby dehydration: the danger of high transepidermal water loss. *Br J Dermatol* 1993;129(1): 86–8.
155. Garty BZ, Metzker A, Nitzan M. Hypernatremia in congenital lamellar ichthyosis. *J Pediatr* 1979;95(5 Pt 1):814.
156. Jones SK, Thomason LM, Surbrugg SK, et al. Neonatal hypernatraemia in two siblings with Netherton's syndrome. *Br J Dermatol* 1986; 114(6):741–3.
157. Turpeinen M. Influence of age and severity of dermatitis on the percutaneous absorption of hydrocortisone in children. *Br J Dermatol* 1988;118(4):517–22.
158. Feinblatt BI, Aceto T Jr, et al. Percutaneous absorption of hydrocortisone in children. *Am J Dis Child* 1966;112(3):218–24.
159. Chiaretti A, Schembri Wismayer D, Tortorolo L, et al. Salicylate intoxication using a skin ointment. *Acta Paediatr* 1997;86(3):330–1.
160. Carlidge PH, Fox PE, Rutter N. The scars of newborn intensive care. *Early Hum Dev* 1990;21(1):1–10.
161. Prizant TL, Lucky AW, Frieden IJ, et al. Spontaneous atrophic patches in extremely premature infants. *Anetoderma of prematurity. Arch Dermatol* 1996;132(6):671–4.
162. Garzon MC, Drolet BA, Baselga E, et al. Comparison of infantile hemangiomas in preterm and term infants: a prospective study. *Arch Dermatol* 2008;144(9):1231–2.
163. Kleinman ME, Greives MR, Churgin SS, et al. Hypoxia-induced mediators of stem/progenitor cell trafficking are increased in children with hemangioma. *Arterioscler Thromb Vasc Biol* 2007;27(12):2664–70.
164. Mayer M, Minichmayr A, Klement F, et al. Tocolysis with the beta-2-sympathomimetic hexoprenaline increases occurrence of infantile haemangioma in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2013;98(2):F108–11.
165. Doege C, Pritsch M, Fruhwald MC, et al. An association between infantile haemangiomas and erythropoietin treatment in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2012;97(1):F45–9.

Neonatal Skin Care and Toxicology

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Introduction

The skin of the neonate has a defective skin barrier relative to an older child. The neonate is extremely vulnerable to damage by environmental agents such as harsh detergents, some topical oils and other irritant chemicals. These agents can interact with genetic tendencies such as *FLG* gene variants¹ and lead to the development of compromised barrier function, and may contribute to the development of *atopic dermatitis* (AD).² For some infants, this is the first step along the *atopic march*; the development of one or more of food allergy, allergic asthma, and allergic rhinitis.³ Evolving perspectives on barrier dysfunction in neonates has led to the idea that there may be a window of opportunity in the first few months of an infant's life to change the environmental agents that their skin is exposed to, in order to maximize skin health, prevent the breakdown of the skin barrier, reduce the development of AD and potentially minimize the atopic march.⁴ These environmental changes could involve the use of optimally formulated wash products, emollients and the removal of all other irritant substances that could damage the skin barrier. Early clinical trials work has been performed, and future research may guide optimal infant skin care from birth.⁵

Structure and function of neonatal skin

As discussed in Chapters 1, 2 and 4, there are structural and developmental differences in the skin of adults, full-term infants and premature neonates. The epidermis develops throughout the second trimester of pregnancy and reaches structural maturity in the third trimester, somewhere between 30 and 37 weeks' gestation.⁶ At this time, a well-defined *stratum corneum* (SC), or 'horny layer', is observed. The intact SC forms the primary barrier to the penetration of irritants, allergens and invading bacteria through the skin, henceforth referred to as the *skin barrier*.⁴ At about 26 weeks' gestation, the epidermis is thin, consisting of only a few cell layers with a poorly formed SC.⁷ Skin barrier function is positively correlated with gestational age during the period of SC maturation.⁸ For instance *transepidermal water loss* (TEWL), an indicator of permeability barrier function,⁹ is 10–15 times higher at 25 weeks' gestation compared with a term infant. Infants less than 24 weeks' gestation have a minimally protective SC at birth, where TEWL is similar to the free evaporation of water.^{7,8} Under these conditions, evaporative heat loss is thought to exceed resting heat production. In addition, their ratio of body surface area to weight is up to five times that of an adult.¹⁰ Premature infants also have an attenuated layer of subcutaneous fat and nonfunctional eccrine glands at birth, which together lead to compromised thermoregulatory capabilities.¹¹

After abrupt exposure to the xeric, postnatal world, premature skin matures rapidly over 2–8 weeks, taking significantly longer for the most premature and lowest-birthweight neonates.¹² Until the epidermis reaches maturity, premature infants are much more susceptible to fluid/electrolyte disturbances, percutaneous absorption of topically applied agents, and percutaneous infection, as a result of inadequate skin barrier function.⁷ Moreover, while the SC is generally considered 'visually mature' in the full-term neonate, recent evidence suggests that the skin barrier does not achieve 'optimum' performance (or functional maturity) for a number of months following birth.¹³ This period of adaption to the extrauterine environment is characterized by a number of changes in the biophysical properties of the skin that differentiate it from adult skin.

Structurally, the thickness of the SC in infants aged up to 24 months is on average 30% thinner when compared with adults.¹⁴ In addition, the thickness of the supra-papillary epidermis is 20% thinner. Similar, lower, and higher TEWL readings have all been reported at different body sites in groups of infants at varying ages compared with adults. Differences in methodology, equipment, test site, and the study populations all contribute to the disparity between TEWL measurements.^{2,8,13} Furthermore TEWL readings in infants are more varied compared with adults, suggesting that infant skin is in a state of flux.¹⁵ Nikolovski and colleagues reported that, in addition to elevated TEWL on the forearms, water absorption and desorption rates were higher, and that there is an altered distribution of water throughout the SC.¹⁵ SC hydration (SCH) is reduced in term infants compared with adults, but increases with increasing postnatal age, resulting in higher, more varied, levels in infants (3–12 months old) compared with adults.^{8,13}

The water-handling properties of the infant SC appear to be very different to those of an adult. One of the causes of this may be the reduced amount of *Natural Moisturizing Factor* (NMF) found within the SC of infants compared with adults.¹⁵ NMF is a collection of hygroscopic compounds involved in moisture retention, the levels of which correlates with TEWL and SCH/clinical dryness.^{16–19} Components of NMF, including urocanic acid and lactic acid, also play a role in maintaining the acidic pH of the skin surface.^{16,17,20} Skin surface pH is neutral at birth in humans and only gradually develops an acid pH over a period of 28 days, and in some cases, may not reach normal/adult pH levels until 2 years of age.⁸ SC pH is a key factor governing skin barrier homeostasis, including regulation of desquamation and lipid synthesis.^{21,22} Accordingly, the size of the uppermost corneocytes is 20% smaller in infants (3–24 months) compared with adults, indicating an increased rate of desquamation.¹⁴

The composition and type of lipids in the SC appears to be dynamic during infancy, not least because of the reduced

production of sebum before puberty.^{23,24} Changes in the make-up of the lipid lamellae affect its structure and subsequently, its ability to act as a permeability barrier.²³ Furthermore, certain SC lipids possess important antibacterial properties, the SC levels of which are associated with the skin's susceptibility to infections.²⁵ Coupled with an elevated skin surface pH, which creates a more favorable environment for the growth of pathogenic bacteria, infant skin exhibits a suppressed antimicrobial barrier, which fits with the increased occurrence of skin infections in infants compared with adults.^{8,25}

Taken together, these changes in the biophysical and biological properties of infant skin indicate that the skin barrier undergoes a period of optimization and adjustment over a period of about 12 months, depending on the body site.^{2,13} During this time, the skin is more susceptible to irritant and allergen penetration and bacterial colonization (Fig. 5.1). An inverse relationship has been reported between postnatal age and the percutaneous absorption of isotope-labeled benzoic acid.²⁶ Furthermore, infant skin, generally considered to be 'sensitive', is prone to the development of dermatological conditions including allergic/irritant contact dermatitis and acne infantum.^{12,27} The temporary retardation of skin permeability and antimicrobial barrier function also coincides with the most at-risk period for developing AD, which affects one in five children.^{28,29} Of AD cases, 45% arise during the first 6 months of life, and 60% by the first 12 months.³⁰ Furthermore, Illi and colleagues reported that 43.2% of children with early onset AD were in complete remission by 3 years of age.³¹ This may reflect the progressive optimization of the skin barrier over the first months to years of life (Fig. 5.2).

GENE–ENVIRONMENT INTERACTION

A number of genetic and environmental factors are known to interact producing negative consequences for the structure and function of the skin barrier,³² especially during the period of postnatal skin development. *FLG* gene mutations resulting in loss of functional filaggrin and its downstream products are the most significant genetic risk factors for the development of AD identified so far, and account for between 15% and 50% of cases, dependent on severity.^{1,33} Carriers of *FLG* loss-of-function mutations with AD exhibit a more pronounced skin barrier defect, characterized by elevated TEWL, increased skin surface pH and decreased SCH, compared with AD patients without these mutations.^{17,18} Having an *FLG* loss-of-function mutation likely affects the development of the skin barrier from birth, but alone may not lead to AD; additional genetic and environmental factors are implicated (Fig. 5.3).³³

Washing the skin with soap and harsh detergents is known to exacerbate AD and other dry skin conditions, especially where the wash water is hard.^{34,35} A single wash with soap or the anionic surfactant *sodium lauryl sulphate* (SLS) elevates TEWL and skin surface pH and decreases SCH. Washing with hard water leads to increased soap use and soap deposition on the skin, leading to increased dryness (decreased SCH) and irritation.³⁶ Furthermore, hard water contains high levels of free calcium, which has been shown in vitro to inhibit skin barrier repair.³⁷ Combining soap or harsh detergents with hard water is thought to result in exaggerated skin barrier damage and prolonged recovery, which may facilitate the development of conditions involving a skin barrier defect. Indeed, living in a

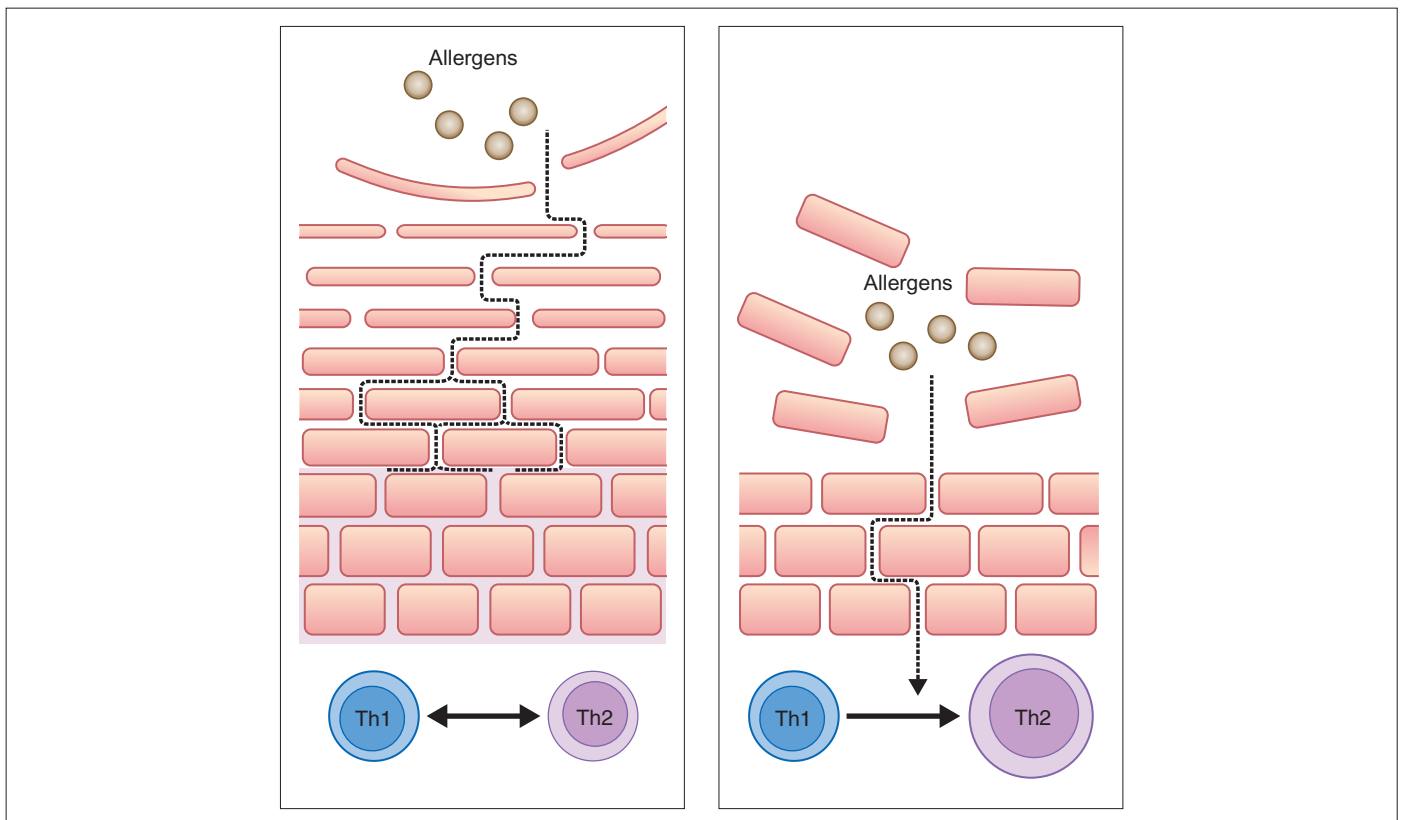


Figure 5.1 Illustration of the SC in adults (left panel) compared with infants (right panel). Adult skin has a higher 'skin barrier reserve' (indicated in purple shading) to protect against environmental challenge. Allergen penetration triggers T helper (Th) type 2 (Th2) cytokine production and thereby potentiates allergic inflammation.

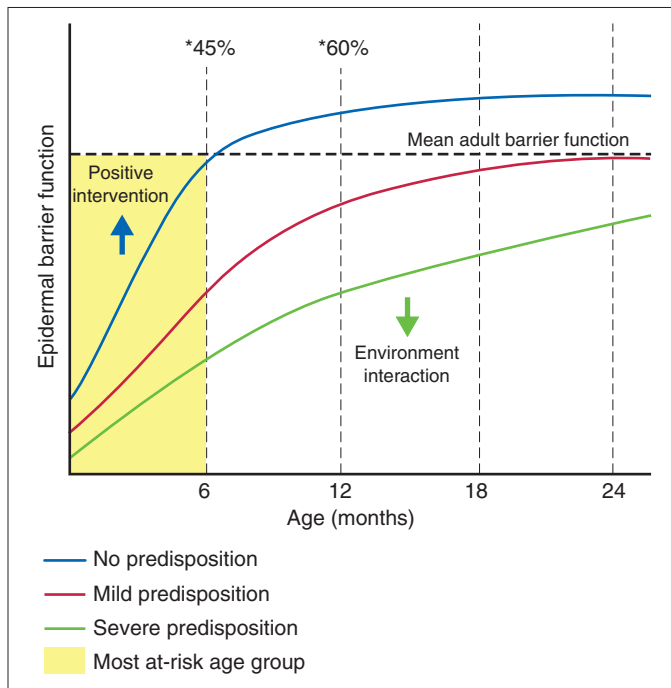


Figure 5.2 An illustrative representation of the proposed development of AD with age. Skin barrier function, assessed by TEWL, does not achieve adult status until after 1 year of age.¹⁵ The SC does not appear to reach maturity on average until after 24 months.¹⁴ The determination of mean adult barrier function (dotted line) is based on normal-appearing volunteers (no clinical signs of AD) who may or may not have an underlying predisposition to a defective skin barrier. A predisposition to a defective skin barrier, the severity of which is thought to be dependent on gene–gene (and gene–environment) interaction, is thought to delay skin barrier development (green and red lines), compared to having no predisposition (blue line). The function of the fully developed barrier is similarly dependent on the inherited predisposition and will determine the life-long susceptibility of an individual to environmental insults. *45% of AD cases will arise by the age of 6 months, and *60% by 12 months.³⁰ The prevalence of AD in the first 2 years of life is 21.5%.³¹ Positive intervention that shifts skin barrier function towards adult levels is expected to decrease the risk of developing AD (blue arrow).

hard water area is significantly associated with increased risk of developing AD.^{38,39} A clinical trial in 2008 reported no effect on the severity of AD associated with the installation of a water softener.⁴⁰ The study did not address, however, the role of wash product interaction with the wash water, the effect of the intervention on development of AD or the nature of the intervention itself (the water softening systems used do not remove all calcium ions, unlike ultrapure water softeners, and do not alter the alkalinity of the wash water). Further research is required to elucidate the role of water hardness. Current guidelines for the treatment of AD recommend the avoidance of soap and harsh detergents, such as SLS along with other negative environmental factors.^{41,42}

In infants, saliva, nasal secretions and some foods are important environmental factors that interact with genetic variants to exacerbate the skin barrier defect.⁴³ Saliva contains proteases and lipases and has a pH of 7.42 (± 0.4) with a substantial buffering capacity.⁴⁴ This provides an optimal pH for protease activity and therefore facilitates skin barrier breakdown. Similarly, breast milk has a pH of 7.29 (± 0.19),⁴⁵ and nasal secretions have a pH of 6.91 (± 0.06),⁴⁶ optimal for protease activity. The combination of saliva, breast milk and nasal secretions caught under a pacifier in a baby with AD leads to a localized ‘drooling dermatitis’ around the mouth and onto the cheeks.⁴³ A combination of adverse environmental factors also contributes to diaper (napkin) dermatitis; urine and feces in conjunction with diaper occlusion, yields elevated skin surface pH and are the sources of additional degradatory proteases and lipases.⁴⁷ The interaction of these negative factors at the diaper area has been shown to affect development of the skin barrier at this site.

Drooling dermatitis may play a role in the development of food allergy. The route of sensitization to some food allergens, such as peanuts, is thought to be through the skin rather than by ingestion.⁴⁸ This supports the observation that the development of AD is often linked to the development of other atopic conditions, including food allergy and asthma.³ The increased risk of further progression along the atopic march highlights

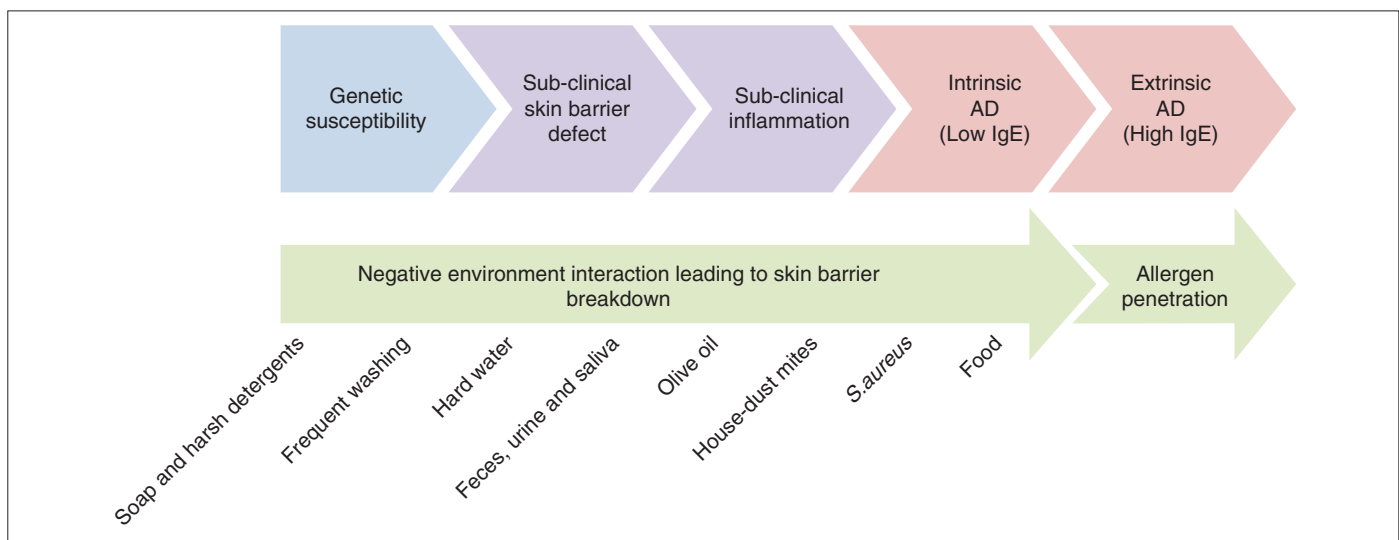


Figure 5.3 Gene–environment interaction and the progression of AD. The course of AD begins with a genetic susceptibility (blue) to a defective skin barrier, which alone does not lead to the development of disease. Negative environmental factors, discussed in the text, interact with genetic factors to determine the sub-clinical skin barrier defect (purple). Theoretically this sub-clinical state is reversible by maintaining a positive environment. Environmental interaction (green arrow) with the skin barrier defect then drives disease progression through to the presentation of clinical disease (pink). A genetic predisposition to a reduced inflammatory threshold would also promote disease progression. Allergen penetration, from food for example, (green arrow) through a defective skin barrier marks the progression from non-atopic disease, with low serum IgE (intrinsic or non-atopic AD), to atopic disease, with high serum IgE (extrinsic or true atopic AD).

the importance of more effective treatment of dermatitis in infants. In the case of drooling dermatitis, avoiding pacifiers and the use of barrier emollients to reduce epidermal damage by saliva (and some foods) should be combined with effective cleansing of the face using products that do not damage the skin barrier.

The continued development (optimization) of the skin barrier and the interplay of negative environmental factors affecting infant skin, raise the importance of how our skin is cared for during the first 2 years of life. While we cannot change the genetics of a neonate or infant, we can modify environmental exposures to help prevent further damage to the skin barrier.

Skin care practices

SKIN CLEANSING

For both children and adults, bathing is a hygienic necessity. The goal of hygiene is the preservation of skin health. However, there is a balance between cleansing the skin and preservation of its homeostatic properties such as skin barrier integrity.⁴⁹ Cleansing is essential to remove pathogenic bacteria such as those from feces. Feces, saliva and other body secretions contain enzymes such as lipases and proteases that breakdown the skin barrier. However, frequent bathing of infants is more of a cultural and aesthetic practice that allows for tactile interaction with the caregiver. Benefits must be carefully considered along with the detrimental effects that can occur with bathing, especially in premature infants.^{49,50}

A balance needs to be reached between the frequency of bathing to achieve optimal cleansing and maintaining an intact skin barrier. For neonates, bathing can lead to hypothermia, increased oxygen consumption, respiratory distress, and destabilized vital signs.⁵¹ Therefore, the first bath should be delayed until after vital signs and temperature have remained stable for at least 2–4 h.^{52,53} Immersion bathing, when feasible, may be beneficial from a developmental perspective. It is more soothing, and can promote enhanced sleep,^{54,55} and in studies, was not associated with significant differences in oxygen saturation, respiratory rate, or heart rate in premature infants of less than 32 weeks' gestation.⁵⁶ The water level should be high enough to cover the infant's entire body to aid temperature control and decrease evaporative heat loss. The optimal temperature of bath water is 100.4°F, which should always be accurately measured. Second-degree burns have been reported after immersion into overly hot bath water tested only by touch.⁵⁷ Sponge bathing with a moistened cotton ball or cloth is an acceptable alternative. Immediately after bathing, the infant's skin should be gently towel dried and a head covering applied.⁵²

Vernix caseosa, composed of sebaceous gland secretions, desquamated skin cells, and shed lanugo hairs,⁵⁸ is negligible in preterm infants. Vernix need not be removed,⁴⁹ as this layer may aid in thermoregulation, hydration, bacterial protection, and wound healing.^{58–61}

The first bath should be given respecting universal precautions to limit contact with transmissible pathogens. The optimal frequency of bathing is open to debate.^{62–64} Research suggests that bathing twice a week will not affect TEWL or skin surface pH, assuming that mild products are used,⁶⁵ and as such, Blume-Peytavi and colleagues recommend that bathing take place no more frequently than every other day.¹³

The use of water alone or water with added skin cleaning products for bathing has led to considerable debate.⁶⁶ Soaps and

cleansers containing harsh detergents, such as SLS increase skin surface pH and reduce SCH.⁶⁷ Conversely, washing with tap water alone leads to the extraction of water-soluble metabolites from the skin, including NMF, and causes mild irritation and increased skin dryness. Furthermore, water alone is ineffective at removing fat-soluble substances from the skin.⁶⁸ The surfactants in cleansers are required to remove these potential fat-soluble irritants. A balance is therefore required between effective cleansing and the need for the mildest surfactants.⁶⁹ SLS is a very effective cleanser, however it is very irritating to the skin, partly associated with its alkaline property. Wash products designed for use on babies' skin contain very mild surfactant complexes and are buffered to skin pH in order to minimize the negative effects on the skin barrier associated with alkaline wash products.⁶⁹

The use of cleansing products compared with water alone for bathing newborns has been subject to a systematic review,⁷⁰ which focused on two trials. One study⁷¹ comprised of four trial arms, including washing twice weekly with a wash gel product; bathing twice weekly with water, then applying a cream; bathing with wash gel and applying cream after bathing; and bathing with water only. The second study⁷² compared two different liquid cleansers with water for bathing infants. The results of these studies indicated no harm to skin barrier function with the tested cleaning agents, although the number of babies in each treatment arm was small.⁷⁰ A large UK-based trial of a mild pH 5.5 liquid SLS-free cleanser versus water alone in bathing neonates for the first 28 days showed essentially no differences in TEWL, hydration, skin surface pH and clinical observations.⁷³ Skin hydration was raised in the cleanser arm at 14 days postnatal (ITT: mean wash score 49.7 (SD 9.2) vs water 46.7 (SD 8.4), $p=0.02$, 95% CI -5.46 to -0.43), but was equal to those in the water group at 28 days postnatal.

There have been no studies to support the routine use of antiseptics. The once-conventional use of antimicrobial cleansers for routine infant bathing diminished following recognition of the toxicity risks. Hexachlorophene was widely used prior to 1975, and was subsequently associated with serious adverse reactions in infants, including fatal neurotoxicity. There has been only one subsequent report of an infectious complication possibly linked to a change in bathing with nonantiseptic cleanser.⁷⁴ The other significant problem with any form of antiseptic is that it can interfere with the acquisition and evolution of normal flora, which may influence colonization with pathogenic bacteria and/or fungi.^{75,76}

Care of the infant scalp and hair follows the same principles as skin care. The same or similar gentle liquid cleansers may be used.⁷⁷ 'Baby' shampoos are distinguished by a low ocular irritation index and a pH and saline concentration similar to those of tears.⁴⁹ This is achieved by using very mild surfactant complexes and buffers in a similar approach to body wash products.⁷⁸ Allergic contact dermatitis from cleansing products, including shampoos, is rare,⁷⁹ as they have very brief contact with the skin before being rinsed off.

Minimal nail care is needed in the neonatal period. Fingernails should be trimmed to limit self-inflicted excoriation, avoiding close trimming that can cause bleeding and lead to infection.⁸⁰

EMOLLIENTS

Emollients in their simplest form produce a layer of oil over the surface of the skin that traps water underneath it. This water

passes back into the dehydrated corneocytes and as a result, they swell up closing gaps between the corneocytes. This is therefore purely an artificial and temporary repair of the defective skin barrier,⁸¹ as such effective use requires frequent application on about 150–200 g per week in young children.⁴²

An ointment containing just oil is the simplest form of emollient; examples include liquid paraffin, white soft paraffin, yellow soft paraffin and mixtures such as 50/50 white soft paraffin and liquid paraffin. These mineral oils are inert, are highly purified and as a result, are extremely unlikely to cause cutaneous reactions.^{82,83} This is why mineral oils are the basis of the majority of emollient formulations and used as the base of many medicinal and wash products. Liquid paraffin is useful as an emollient and massage oil and is not very occlusive. In contrast, white soft paraffin is very occlusive and can lead to folliculitis eruptions, especially in hot weather.

As soon as water is added into a formulation, whether it is an ointment or cream, then emulsifiers are needed to form a stable formulation of the oil and water. Emulsifiers are surfactants (detergents) and as a result, can damage the skin barrier.⁶⁹ The very harsh anionic surfactant SLS for example, solubilizes SC lipids, denatures keratin and elevates skin surface pH resulting in disturbed skin barrier homeostasis. It is therefore reasonable to use emollient cream and ointment formulations that contain the mildest emulsifiers, which will cause the least damage to the skin barrier.⁸⁴ Some emollients, creams, and ointments contain SLS, despite its use as a standard skin irritant in patch-testing. Examples include aqueous cream BP, emulsifying ointment and many proprietary emollients. The use of aqueous cream BP as a topical emollient was found to damage the skin barrier; an effect associated with the presence of SLS in its formulation.^{84–86} Furthermore, aqueous cream BP was associated with irritant cutaneous reactions and exacerbation of the condition in the majority of infants and children with AD in a pediatric dermatology clinic.⁸⁷

The effect of a simple petrolatum cream can be enhanced by adding humectants such as glycerol, urea, lactic acid and sodium pyrrolidone carboxylic acid, some of which are naturally found in the skin as part of NMF.^{88–90} Humectants attract and hold water in the SC,⁹¹ and therefore compensate for the reduced levels of NMF found in infant skin. The ability of an emollient to repair a defective skin barrier may also be enhanced by the addition of ingredients that contribute to enhancement of the lipid lamellae, including ceramides and particular fatty acids such as linoleic acid.⁸¹

The use of emollients is, in general, associated with improvement in skin dryness, pruritus and skin barrier function.⁴¹

However, there is a very limited evidence base for the efficacy of emollients.^{42,92} Randomized controlled trials published in recent years in established AD suggest that the use of certain ‘complex’ emollients can be steroid sparing, reduce the severity of AD and delay relapse of the condition.^{90,93} Importantly, emollients are not all the same, and depending on their formulation can have very different effects on the skin (Table 5.1). While aqueous cream, with an old formulation comprising a harsh surfactant and no humectant, is minimally hydrating and damages the skin barrier, newer more sophisticated formulations containing humectants considerably improve hydration while being mild. It is the positive effects of certain emollients that has raised the possibility of emollient therapy from birth as a promising intervention for the prevention of AD in high-risk cases.⁹⁴

INFANT MASSAGE

Infant massage, a tradition in many cultures, has recently been repopularized. Infant massage has many reported and theoretical benefits, including increased interaction and bonding opportunities between infants and parents, improved parental understanding of the infant’s behavior, and reduced parental stress.^{95,96} Variables studied in hospitalized premature infants include decreased motor variability and distress, and enhanced weight gain and development, leading to reduced length of stay.⁹⁷ However, an evidence-based review in 2004 did not recommend this practice,⁹⁸ calling into question the methodological quality of the studies.

Interestingly, several studies have suggested that weight gain associated with infant massage may be due primarily to percutaneous absorption of essential fatty acids from the massage oil. Animal studies first documented a reversal of fatty acid deficiency in rats treated with cutaneous application of essential fatty acid (EFA)-rich safflower oil.⁹⁹ This was not reproduced in neonates treated with sunflower seed oil,¹⁰⁰ but subsequent studies in premature and full-term infants have shown positive effects of oil massage. Weight and length gain velocity were statistically increased in newborns receiving oil massage four times a day for the first 31 days of life.¹⁰¹ Infants massaged with safflower oil had significant rises in serum essential fatty acids, including linolenic acid and arachidonic acid, whereas infants massaged with coconut oil had increases in saturated fats.¹⁰²

Certain natural oils have also been reported to soften the skin and provide moisturization,¹⁰³ possess antimicrobial activity,^{104–106} display anti-inflammatory properties^{107,108} and reduce skin irritation.¹⁰⁹ Randomized controlled trials on the clinical

TABLE 5.1 Key differences between emollients

Properties of dry skin in infants	Different properties of emollients	Effects on the skin
Reduced levels of natural humectants (NMF)	Humectant (such as urea, glycerol and lactic acid)	Humectants bind to water in the SC and improve the hydrating effects of emollients
Abnormal lipid lamellae	Physiological lipids (including ceramides, cholesterol and free fatty acids)	Some physiological lipids help repair the defective lipid lamellae and improve skin barrier function
Increased susceptibility to irritants	Surfactant system (required to emulsify oil in water formulations)	Harsh surfactants like SLS can damage the skin barrier and irritate the skin, whereas some surfactant complexes are as mild as water
Elevated skin surface pH	Product pH and buffering capacity	Modification of skin surface pH with subsequent effects on skin barrier homeostasis. Products that increase skin surface pH are associated with increased proteolytic breakdown of the skin barrier.

effect of topically applied sunflower seed oil and almond oil have reported significant benefits, such as reduced nosocomial infections and quicker recovery of dermatological conditions.^{104,105,110,111} These benefits can be, at least in part, linked to improved skin barrier function.^{110,112} Notably however sunflower seed oil was found to improve skin barrier integrity, whereas olive oil had the opposite effect, being associated with skin barrier damage and mild irritation.^{112–114} When a panel of 14 natural oils were compared for their ability to prevent experimentally induced irritant contact dermatitis in humans, positive effects (based on clinical scoring of irritation, TEWL and chromametry) were associated with oils containing low oleic acid and high linoleic acid.¹¹⁵ Olive oil contains 55–83% oleic acid, a skin penetration enhancer that at 5% significantly increases TEWL when applied to the skin.¹¹⁶ In contrast to olive oil, the predominant fatty acid in sunflower seed oil is linoleic acid. Linoleic acid has been shown to exert positive effects on the skin barrier,¹¹² attributed to its potent activation of peroxisome proliferator-activated receptor α (PPAR α), involved in regulating keratinocyte proliferation, inflammation and skin barrier homeostasis. The choice of massage oil therefore has significant consequences for the condition of the skin and the risk of bacterial sepsis.

The type of oil used varies according to country. This has led to a number of investigations of the impact of different types of oils (e.g., mustard, almond, sesame, herbal, mineral, coconut, vegetable and sunflower seed) on newborn skin.^{104,111,117–121} In the UK, a recent survey of oil use found that 52% of maternity/neonatal units recommend the use of oil for infant skincare.¹²² Olive oil was most frequently recommended (82%) followed by sunflower seed oil (21%). Further qualitative work found that midwives and health visitors regularly recommend the use of natural oil for babies' dry skin.⁶⁶ Their preference is influenced by their belief in the safety of natural oils and the desire to offer a cheap solution to the problem of dry skin. This opinion is in the presence of evidence indicating that olive oil causes significant damage to the skin barrier. In view of the positive effects of mineral oil on the skin barrier⁸² an RCT comparing its use with other oils is needed.

In light of the positive and negative effects of topical massage oils, their complex and variable composition, and the potential for sensitization,¹²³ further research is required to ensure that the oils used for massage are safe and effective.

DIAPERING AND DIAPER CARE PRODUCTS

The first disposable diapers marketed in 1963, had an absorbent core of cellulose fluff. In the mid-1980s, a superabsorbent core material containing a cross-linked sodium polyacrylate was developed. This material, contained in all superabsorbent disposable diapers, transforms and holds fluid within a gel and has the capacity to absorb many times its own weight. As a result of this, pseudoanuria has been reported in an infant, because of the inability to feel moisture on a superabsorbent diaper.¹²⁴ Urine output, monitored by weighing diapers, can also be erroneous if diapers are allowed to remain open under a radiant warmer.¹²⁵

Irritant diaper dermatitis is rare in the immediate neonatal period, but increases in incidence over the first month,¹²⁶ with overall prevalence between 4% and 15%.¹²⁷ There is a complex interplay in the occlusive diaper environment, with many components contributing to the pathogenesis of diaper dermatitis.

Excessive hydration leads to maceration and increased skin permeability. Now prone to injury, the addition of alkaline urine changes the normal protective acidic pH of the skin¹²⁸ and permits the growth of microorganisms, including *Candida albicans*, *Staphylococcus aureus* (*S. aureus*), and *Streptococcus*.¹²⁹ This pH also activates fecal lipases, endogenous and exogenous proteases, and bile salts, which can lead to further injury.^{21,130}

Superabsorbent diapers are clearly superior to cloth diapers in preventing irritant diaper dermatitis.¹³¹ Disposable diapers effectively reduce maceration, help create a favorable pH, decrease exposure to urine and feces, and better contain enteric pathogens.^{132,133} Other contactants in the diaper area may not have such a favorable profile and can worsen the factors that lead to diaper dermatitis. Topically applied medications in the diaper area are also more readily absorbed and can lead to irritation, sensitization, and percutaneous toxicity.

The use of medicated baby wipes has increased over recent years for diaper area cleansing of term newborns.¹³⁴ However, concerns have been raised related to the suitability of these products and their potential links to dermatitis.¹³⁵ A wide range of baby wipe products are available, with varying formulations.¹³⁶ Older formulations, in particular, include harsh surfactants, alcohol and fragrance, which have been associated with contact dermatitis in adults.^{135,137,138} More recent product development has led to wipes free from alcohol, fragrance, with appropriate surfactants and preservatives, and pH adjusted to 5.5. These more recent formulations have been subject to clinical trials with newborn infants. Two small scale studies^{139,140} indicated that wipes are suitable for use with term infants in the newborn period, but were methodologically limited by sample size. This has been confirmed by a recent assessor-blinded randomized controlled trial by Lavender and coworkers,¹³⁶ focusing on healthy term neonates ($n = 280$) from birth to 28 days postnatal. This study found one wipe formulation, with low pH 5.5 and alcohol and fragrance free, had an equivalent effect to water on skin hydration, TEWL or pH versus water. While dermatitis has always been a concern, there was no evidence of any increase in erythema or skin breakdown in any of the clinical measures used, although data from maternal observations of diaper area skin suggest a higher rate of low-grade diaper rash in babies cleansed with water and cotton wool ($p = 0.025$). The authors conclude that the wipe formulation used in the trial (pH 5.5, alcohol free, fragrance free) is equivalent to water and cotton wool for neonatal diaper area cleansing.

ULTRAVIOLET PROTECTION AND THERMAL INJURY

The overall density of melanocytes in skin is greater in children than in adults, but melanin production is limited and melanocytes in children may be more susceptible to ultraviolet (UV)-induced damage.¹⁴¹ In addition, infants and children have not had the gradual UV exposure that stimulates facultative pigmentation. For these reasons, pediatric patients are more susceptible to the damaging effects of excessive exposure to sunlight.

A sunscreen is a compound that absorbs, reflects, or scatters the harmful spectrum of UV light (290–400 nm). An increasingly wide variety of sunscreen products are available. Ingredients that reflect and scatter a large portion of the solar spectrum, including UVB, UVA, and visible light, are zinc oxide and titanium dioxide.

The safety of topically applied sunscreens has not been established for infants under 6 months of age, but the theoretical risk of toxicity is low. Concerns in the past have focused on neonatal metabolism of *p*-aminobenzoic acid (PABA), a folic acid analog with structural similarities to those of the sulfonamides. A safe first-line strategy for sun protection in infants is sun avoidance, and the use of appropriate clothing, with physical sunscreens containing zinc oxide and/or titanium dioxide applied to areas that cannot be adequately covered with clothing such as the face and hands.

Percutaneous absorption and toxicity

An infant's immature skin barrier, coupled with a high ratio of body surface area to weight, significantly increases the risk of percutaneous absorption. Numerous reports have documented percutaneous poisoning from agents applied to the skin of infants and children (Table 5.2). Further compounding this risk are the developmentally distinct aspects of pediatric pharmacokinetics: absorption, tissue distribution, metabolism, and detoxification.^{152,153} In addition, toxicologic data are lacking for most of these topically applied agents, especially for infants and children, a group known as therapeutic orphans.^{11,154} Revered clinicians have historically overlooked the potential for percutaneous poisoning in designing therapy for infants. This was evidenced by an epidemic of neonatal cyanosis in London in the late 1800s. At that time, cloth diapers were labeled with aniline dye stamps. The imprint of the stamp on the perineum and buttock of one of the affected infants was a clue to the diagnosis. Despite this discovery, diapers labeled with aniline were used for decades, resulting in at least six infant deaths.¹⁵⁵

Another example is Cooke's 1926 review of diaper dermatitis. Here, he recommended a rapid and permanent 'cure' for 'ammoniacal' dermatitis by rinsing diapers in either dilute mercuric chloride or saturated boric acid solution.¹⁵⁶ Over the last 70 years, published accounts have served to document only the most severe toxicities – in some cases manifesting as nursery epidemics of obvious clinical illness or deaths.

With regard to topical therapy in infants, both active ingredients and vehicles are important to consider. The vehicle affects the absorption of the active medication. Hydrophilic agents are able to penetrate the lipid bilayer better than water-soluble compounds. Topically applied lipids also enhance epidermal hydration, widening intracellular bonds and facilitating enhanced absorption.¹⁵⁷ Emulsifiers are required to enable the mixing of aqueous and oil components in a product and help make the product easier to apply to the skin. Fragrances may be added to enhance product appeal. Preservatives are bacteriostatic compounds required for any product that contains an aqueous component.

Unpreserved, or poorly preserved creams, lotions and wash products, are an important source of bacteria and fungi that can cause infections in neonates.^{142,158–163} A wide range of bacteria and fungi have been isolated from these unpreserved products, including *S. aureus*, *Enterococcus* spp., *Pseudomonas aeruginosa*, *Candida albicans* and *Trichophyton* spp. In one study, 19 unpreserved creams were challenged with bacteria. All 19 grew bacteria after 48 h and the bacterial count was up to 22 million colony-forming units per gram.¹⁶¹ This paper is important because it demonstrated that every container of poorly preserved or unpreserved cream that became contaminated with bacteria led to the production of millions of bacteria,

TABLE 5.2 Reported hazards of percutaneous absorption in infants and children

Compound	Product	Toxicity
Alcohols ^{124,125}	Skin antiseptic	Cutaneous hemorrhagic necrosis, elevated blood alcohol levels
Aniline ¹⁶	Dye used as a laundry marker	Methemoglobinemia, death
Adhesive remover solvents ¹²⁹	Skin preparations to aid in adhesive removal	Epidermal injury, hemorrhage and necrosis
Benzocaine ¹⁴²	Mucosal anesthetic (teething products)	Methemoglobinemia
Boric acid ²⁴	Baby powder, diaper paste	Vomiting, diarrhea, erythroderma, seizures, death
Calcipotriol ¹⁴³	Topical vitamin D ₃ analogue	Hypercalcemia, hypercalcemic crisis
Chlorhexidine ¹²⁰	Topical antiseptic	Systemic absorption but no systemic toxic effects; skin burns in preterm infants
Corticosteroids ¹⁴⁴	Topical anti-inflammatory	Skin atrophy, striae, adrenal suppression
Diphenhydramine ¹⁴⁵	Topical anti-pruritic	Central anticholinergic syndrome
Lidocaine ⁸⁵	Topical anesthetic	Petechiae, seizures
Lindane ¹⁴⁶	Scabicide	Neurotoxicity
Mercuric chloride ¹⁴⁷	Diaper rinses, teething powders	Acrodynia, hypotonia
Methylene blue ¹⁴⁸	Amniotic fluid leak	Methemoglobinemia
<i>N,N</i> -dimethyl- <i>m</i> -toluamide (DEET) ¹¹³	Insect repellent	Neurotoxicity
Neomycin ¹⁰⁸	Topical antibiotic	Neural deafness
Phenolic compounds (pentachlorophenol, hexachlorophene, resorcinol) ¹⁹	Laundry disinfectant, topical antiseptic	Neurotoxicity, tachycardia, metabolic acidosis, methemoglobinemia, death
Phenylephrine ¹³	Ophthalmic drops	Vasoconstriction, periorbital pallor
Povidone-iodine ¹²²	Topical antiseptic	Hypothyroidism
Prilocaine ⁸⁶	Topical anesthetic	Methemoglobinemia
Salicylic acid ¹⁴⁹	Keratolytic emollient	Metabolic acidosis, salicylism
Silver sulfadiazine ^{137,139}	Topical antibiotic	Kernicterus (sulfam component), agranulocytosis, argyria (silver component)
Tacrolimus ¹⁵⁰	Topical immunomodulator	Elevated blood levels of immunosuppressive medication
Triple dye (brilliant green, gentian violet, proflavine hemisulfate) ⁷¹	Topical antiseptic for umbilical cord	Ulceration of mucous membranes, skin necrosis, vomiting, diarrhea
Urea ¹⁵¹	Keratolytic emollient	Uremia

which could cause severe infections if applied to the skin of a neonate. Unpreserved creams can become contaminated with bacteria from an infant's skin if the parent puts their hand into the pot of cream then onto the infant's skin and back into the pot of cream again.^{143,144} The bacteria can then multiply in the unpreserved cream and when re-applied to the infant's skin, lead to life-threatening infections. In one case report, a 1-year-old child with AD developed life-threatening *S. aureus* infection following the repeated application of an unpreserved cream to the skin.^{143,144}

Life-threatening infections have been caused by the use of unpreserved hand lotions on healthcare workers in an intensive care unit (ICU). The unpreserved lotion became contaminated with *Burkholderia cepacia*, which was then transferred from the ICU staff's hands to the patients' skin.¹⁴⁵ There are several other reports of clusters of deaths and serious infections in NICUs following the use of unpreserved/poorly preserved hand lotions and creams.¹⁵⁸

When the microbial challenge to a cream is very high, such as the skin of an infant or child with AD, even a cream preserved with licensed preservatives can become contaminated with bacteria.¹⁴⁴ Ointments are not regarded to be at high risk of contamination because they do not contain water. However, at the surface of an ointment, water can condense and microbial contamination is more likely to occur at this point. An audit of licensed preserved emollient creams and unpreserved ointments in a pediatric dermatology clinic revealed that 53% of the emollient samples were contaminated with bacteria, including *S. aureus*, *Streptococcus*, and *Enterococcus*.¹⁴⁴ As a result, we now advise the parents of infants and children with AD regarding the safe use of licensed emollients, creams and ointments (see Box 5.1).

Table 5.3 reviews products that should be used with caution in newborns based on potential toxicity and side-effects. The best approach is to use topical products with simple vehicles, that are effectively preserved and to be aware of the quantity applied as well as the duration of skin contact.

Special issues in the NICU (see Chapter 4)

SKIN ANTISEPSIS

Skin antiseptics practices such as cord care regimens and the use of antimicrobial washes prior to invasive procedures are used to help control nursery epidemics of localized and invasive streptococcal and staphylococcal infections. Prospective, controlled comparative outcome studies on the safety and efficacy of these practices are lacking.

Common cord care practices include nonintervention ('dry cord care')⁵³ or the use of an antimicrobial agent. The most commonly used antiseptics are isopropyl alcohol, triple dye (brilliant green, gentian violet, and proflavine hemisulfate), povidone-iodine, bacitracin, hexachlorophene, and chlorhexidine. The data regarding control of bacterial colonization and prevention of omphalitis are conflicting.^{74,146–149} Although antiseptic cord care may reduce the risk of colonization and subsequent infection, it exposes infants to potentially toxic and sensitizing agents (see Table 5.2) and delays cord separation. Important variables to consider when selecting antiseptic agents for cord care include efficacy against bacterial colonization and the potential for percutaneous toxicity. With regard to bacterial colonization, chlorhexidine has been shown to be superior to 70% ethanol,¹⁵⁰ hexachlorophene,¹⁵¹ and povidone-iodine¹⁶⁴ in reducing group A streptococcus and *S. aureus*, but not coagulase-negative staphylococci, group B streptococci, or Gram-negative bacilli. Triple dye has been superior to bacitracin ointment,¹⁶⁵ hexachlorophene,¹⁶⁶ and isopropyl alcohol,¹⁶⁷ but may promote colonization with Gram-negative organisms.¹⁶⁸ The efficacy of any topical antimicrobial agent may diminish with prolonged use. As regards toxicity (see Table 5.2), isopropyl alcohol, povidone-iodine, triple dye and hexachlorophene have been shown to have negative effects, but these have not been similarly reported with chlorhexidine.

Chlorhexidine has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria and yeast. It binds strongly to the skin, which may act to reduce its absorption and increase its local efficacy.¹¹ An 0.5–4% aqueous chlorhexidine-containing product appears to be a safe choice for infants.¹⁶⁹ Several products contain chlorhexidine and isopropyl alcohol

BOX 5.1 ADVICE REGARDING THE SAFE USE OF LICENSED EMOLLIENTS, CREAMS AND OINTMENTS

1. Always wash hands before using emollients or ointments
2. Use only licensed medicinal emollients, containing approved preservatives
3. For pump dispensers and tubes:
 - Avoid contact with nozzle
 - Wipe nozzle clean after use
4. For open pots:
 - Before use: decant sufficient emollient into a separate container using a clean spoon
 - Do not put hands into pots of emollient (patient or carer)
5. Use one container of emollient at a time and do not keep opened containers for more than 2 weeks
6. Store opened containers in the refrigerator

TABLE
5.3

Topical agents that should be used with caution in the newborn

Compound	Product	Concern
Ammonium lactate	Keratolytic emollient	Possible lactic acidosis
Benzethonium chloride	Skin cleansers	Poisoning by ingestion, carcinogenesis
Coal tar	Shampoos, anti-inflammatory ointments	Excessive use of polycyclic aromatic hydrocarbons are associated with an increased risk of cancer
Glycerin	Emollients, cleansing agents	Hyperosmolality, seizures
Propylene glycol	Emollients, cleansing agents	Excessive enteral and parenteral administration has caused hyperosmolality and seizures
Triclosan	Deodorant and antibacterial soaps	Toxicities seen with other phenolic products

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at varying concentrations, and cause irritation when impregnated on dressing materials in very low-birthweight infants.¹⁷⁰ Detectable increasing plasma chlorhexidine levels were documented in preterm infants treated with 1% chlorhexidine in an unspecified concentration of ethanol every 4 h for 5–9 days.¹⁷¹ Significant absorption could not be documented in a similar group of infants treated with 1% chlorhexidine in a 3% zinc oxide dusting powder, supporting the role of alcohols in facilitating percutaneous absorption.¹⁷¹ Some commercially available formulations also contain the proprietary pluronics, fragrance, and red dye. Pluronics are added solely to enhance lathering and can cause serious corneal damage.

Povidone-iodine is a common topical antiseptic preparation. It is convenient with single-use preparations. Adverse effects of topically applied iodine have been recognized in infants for decades.¹⁷² They include local skin necrosis, and hypothyroidism due to absorption in four infants treated with iodine-containing ointment on open wounds.¹⁷³ If povidone-iodine is used, it should be in two consecutive applications with drying for at least 30 s to be effective. Any residue should be thoroughly cleansed from the skin after the procedure.⁵²

Alcohol is a commonly used topical antiseptic, which, because of its volatility, rapidly evaporates before absorption. Generous application followed by occlusion can result in significant absorption, and can also enhance the absorption of other concomitantly applied medications, especially through immature or diseased skin. Hemorrhagic skin necrosis due to alcohol has been reported in preterm infants.¹⁷⁴ Additional potential toxicities include metabolic acidosis, central nervous system dysfunction, and hypoglycemia,¹⁷⁵ with acute intoxication reported in infants where isopropyl alcohol has been used for umbilical cord care.¹⁷⁶ Despite their comfortable familiarity and ready availability in single-use pads, the use of alcohol solutions is not recommended in infants, as they are less effective and have more potential side-effects.^{52,177}

The indiscriminate use of topical antibacterial agents is not recommended.¹⁷⁸ Use of topical antimicrobial agents for prophylaxis increases the risks of bacterial resistance and contact sensitization. As they can also disrupt the normal commensal skin flora, their use should be restricted to true cutaneous infections.¹⁷⁹ The potential for subclinical toxicities must be considered by everyone caring for small neonates. When several topical therapeutic options are available, the one with the greatest antimicrobial efficacy and the least potential for toxicity should be utilized. Poisindex® is an extensive, frequently updated, computerized reference source for the identification of potentially toxic compounds.¹⁸⁰

ADHESIVES

Adhesives have many applications in the NICU, but there are also under-appreciated risks (Fig. 5.4). Adhesives are important for securing monitoring and life-saving equipment. They are also a primary cause of skin breakdown, with up to 90% of SC being removed after a single tape stripping from neonatal skin.¹⁸¹ In addition, little is known about the potential for percutaneous toxicity or allergic sensitization from rubber or cyanoacrylate-based products. Despite the routine use of adhesives in the nursery, there are few studies identifying improved products or procedures to minimize associated side-effects.¹¹ Strategies to limit this trauma are outlined in the Association of Women's Health, Obstetric and Neonatal Nurses (AWOHN)



Figure 5.4 This 27-weeks' gestation premature infant receiving phototherapy demonstrates how many exogenous materials are applied to the skin for standard interventions.

guidelines.⁵² They include strictly limiting the area of adhesive application and eliminating the use of bonding agents. Attention should be paid to using smaller pieces of tape, backed with cotton or additional tape, and using alternate, nonadhesive-based products such as hydrogel electrodes. These products may, however, be less reliable in securing equipment and should not be used when secure adherence is critical.

TRANSEPIDERMAL WATER LOSS (TEWL)

TEWL is coupled with evaporative heat loss in infants. In premature infants of less than 30 weeks' gestation, it can be excessive, owing to their limited cutaneous barrier function. Losses range from 40 to 129 mL/kg per day,¹⁸² and this can lead to significant fluid and electrolyte disturbances. The appropriate calculation of replacement fluids can be difficult, as measurable parameters lag behind actual losses.

Several techniques have been reported to minimize heat and water loss in neonates, but three methods have been studied and shown to be effective specifically in limiting TEWL. These include increased ambient humidity, occlusive dressings, and routine use of emollients.

Increased ambient humidity increases water vapor pressure, which inversely decreases evaporative fluid and heat loss.¹⁸³ An environment that can provide high ambient water vapor

pressure (relative humidity >85%), such as a double-walled incubator or servo-controlled humidification incubator, will therefore reduce evaporative water loss through the skin. Conversely, lower ambient water pressure under a radiant warmer increases TEWL.¹⁸⁴ Conventional phototherapy has this effect, however LED phototherapy does not elevate TEWL.¹⁸⁵ While high humidity can improve fluid management in the preterm neonate, recent evidence suggests that skin barrier development following birth is prolonged.¹⁸⁶ Furthermore, increased ambient humidity also increases the theoretical risk of bacterial contamination;¹⁸⁷ therefore, use of this modality should be limited to no more than 1 week.⁵²

Semipermeable, transparent polyurethane dressings have been reported in two studies^{188,189} to effectively decrease TEWL with no increased risk of infection, although this was not the case in a study by Donahue and coworkers.¹⁹⁰ One additional study showed reduced fluid and electrolyte disturbances with decreased mortality associated with the use of this type of dressing.¹⁹¹ This type of dressing, once applied, should not be removed if possible, as removal can lead to significant skin injury.⁵² An alternative is blanketing an infant with a thin, pliable clear plastic wrap, which has been shown to reduce insensible water loss.¹⁹² A wide variety of products and materials is used in diverse ways. The majority of these products are not manufactured or indicated for this purpose, raising several concerns about the inconsistent composition, uncertain shelf-life, the possibility of degradation with prolonged exposure to heat, and the possibility of significant infrared absorption.

Regular, liberal applications of bland, petrolatum-based ointments to the skin surface have also been shown to decrease TEWL, and improve fluid management and the condition of the skin.^{193–196} The effect on decreasing TEWL is greatest immediately following the application of an emollient, but diminishes over 3–6 h. Therefore, to be effective, emollients must be applied at a minimum of every 6 h to limit TEWL.⁵² An evidence-based review conducted during 2003 did not recommend prophylactic ointment use on a routine basis for premature infants due to the increased risk of coagulase-negative staphylococcal infection and any nosocomial infection.¹⁹⁷ Since the publication of this review, a prospective study¹⁰⁵ evaluated the use of two different topical emollients in preterm Bangladeshi infants <33 weeks' gestation. Infants treated with sunflower seed oil were less likely to develop nosocomial infection than controls, but Aquaphor® did not significantly increase or decrease the risk of infection. Both emollients have previously been shown to enhance the condition of the skin barrier.¹⁹⁸ Furthermore, sunflower seed oil was reported to reduce the entry of pathogens from the skin into the bloodstream. As a result of skin barrier enhancement and reduction in nosocomial sepsis, the use of Aquaphor® and sunflower seed oil was associated with significantly reduced mortality rate in preterm infants in Bangladesh.¹¹⁰

Clearly, the use of these techniques to control thermal and fluid losses in small premature infants deserves further study. There is currently no 'best practice' defined for these parameters, the various methods never having been directly compared to one another to fully assess outcomes.

Skin care guidelines

In 1999, the skin care practices in neonatal nurseries were often based in tradition,¹⁹⁹ with wide variability and no consistency

noted in multiple surveys.^{200–202} An evidence-based comprehensive practice guideline was published in 2001.^{52,53,203} This landmark reference includes a validated 9-point scale that rates dryness, erythema, and skin breakdown, which is helpful in monitoring neonates who are at exceptionally high risk for skin problems (Table 5.4).²⁰⁴

Current guidance on skin cleansing has been limited by the lack of available high quality evidence, leading to a number of differing guidelines.^{13,203,205–207} Hence, there has been confusion among health professionals in relation to appropriate advice.⁶⁶ Guidance from the World Health Organization²⁰⁵ is limited to bathing a newborn in warm water, at least 6 h following birth. There is no UK NICE (National Institute for Health and Care Excellence) guidance specifically about neonatal skin care. The NICE Postnatal Care Guidelines²⁰⁷ contain one paragraph about neonatal skin care, which recommends that cleansing agents, lotions or medicated wipes should not be used; using only a mild non-perfumed soap where necessary. In contrast, AWOHNN²⁰³ guidance is more specific and recommends the use of a cleansing wash, with a neutral pH, that has been formulated for use on newborns. An overview of these guidelines is presented in Box 5.2. More recent evidence suggests that wash products should have a low pH around 5.5 in order to have optimal effects on the skin barrier.⁸¹ However, it is important to note that much of this guidance is now out of date and in some cases is incorrect or not evidence-based, for instance where the use of soap is advocated.^{4,67} There have been substantial advances in formulation technology of baby wash products since these guidelines were written and recent trial evidence needs to be taken into consideration in making decisions and advising on newborn skin care practice.^{65,71–73,136,139,140}

TABLE 5.4 AWHONN neonatal skin condition score (NSCS) tool

Dryness
1 Normal, no sign of dry skin
2 Dry skin, visible scaling
3 Very dry skin, cracking/fissures
Erythema
1 No evidence of erythema
2 Visible erythema, <50% body surface
3 Visible erythema, ≥50% body surface
Breakdown
1 None evident
2 Small, localized areas
3 Extensive
Perfect score = 3, worst score = 9

This scoring system, developed for the AWHONN/NANN Neonatal Skin Care Research-Based Practice Project (RBP4) was adapted from a visual scoring system used in a previous study (Lane and Drost, 1993). This tool can facilitate assessment of neonatal skin condition. Adapted from the Association of Women's Health, Obstetric and Neonatal Nurses Evidence-based clinical practice guideline for neonatal skin care. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003; 112: S118–27

BOX 5.2 RECOMMENDATIONS FOR BASIC SKIN CARE OF THE PREMATURE NEWBORN

1. Use adhesives sparingly
 - Place protective dressing at sites of frequent taping (endotracheal and nasogastric tube placement)
 - Use nonadhesive electrodes and change them only when they become nonfunctional
2. Limit bathing
 - Defer initial cleansing until body temperature has stabilized
 - Avoid cleansing agents for the first 2 weeks
 - Use warm water and moistened cotton pledgets in a humid environment
 - Surface cleansing is required no more than twice a week
 - If antimicrobial skin preparation is required, use short-contact chlorhexidine (except on the face)
3. Be aware of the composition and quantity of all topically applied agents
 - This includes antimicrobial cleansers, diaper wipes, adhesive removers, perineal products
 - Dispense from single-use containers, if possible
4. Ensure adequate intake of protein, essential fatty acids, zinc, biotin, and vitamins A, D, and B
 - Be aware that erosive periorificial dermatitis is a sign of nutritional deficiency
5. Consider use of ointment emollient for xerosis or minor skin abrasions
6. Guard against excessive thermal and UV exposure
 - Use thermally controlled water for bathing
 - Avoid surface monitors with metal contacts
 - Use Plexiglas® shielding over daylight fluorescent phototherapy
7. Protect sites of cutaneous injury with the appropriate occlusive dressing
 - Use a film dressing on nonexudative sites
 - Use a foam dressing on exudative wounds
 - Maintain appropriate hydration at the skin–dressing interface
 - Remove necrotic debris with each dressing change

Summary

Term neonates are born with a functional skin barrier that helps to protect the body from the potentially harmful outside environment. The maturity of the skin barrier in preterm infants is dependent on gestational age, however upon birth, the skin rapidly adapts to the extrauterine environment. At this stage, the skin barrier may be functional, however it takes a number of months before it reaches optimum performance, as seen in

young adults.^{2,13} During this period, the skin is most susceptible to damage by negative environmental factors such as soap and harsh detergents, saliva and nasal excretions and urine and feces, for example. Furthermore, the skin is prone to irritant and allergen penetration and invasion by pathogenic bacteria such as *S. aureus*. It is no surprise therefore that the majority of cases of AD arise during this period.³⁰ On a global population scale, perhaps of even greater importance, is that 50–70% of fatal and life-threatening neonatal infections occur in the first week of life.^{11,208}

It is important to view this neonatal period as a window of opportunity to intervene and prevent fatal infections and the development of AD. For instance, the use of certain emollients in preterm infants in Bangladesh resulted in a 30% reduction in mortality.¹¹⁰ Some oils and emollients, such as olive oil and aqueous cream, may have had the opposite effect in such a clinical trial, because they damage rather than repair the skin barrier.^{84,86,112,113} Preliminary studies also suggest that early intervention with certain emollients can help prevent the development of AD.^{5,93,94} Having AD often leads onto other atopic conditions, including asthma, making primary prevention of AD highly desirable. Not only do these studies highlight the possibility of prevention, they also evidence the need for the highest standard of skincare during the first months of life. Only by taking an evidence-based approach can we avoid further damage to the already fragile skin. Traditional practice should be carefully and critically evaluated. For example, olive oil, known for its health benefits when used in cooking, is traditionally used for infant massage, yet recent evidence suggests that it damages the skin barrier.^{112,113} In contrast a lesser-used alternative, sunflower seed oil, has been associated with multiple positive effects on the skin.^{104,105,110,112,113,198,209} Natural products are very complex, containing multiple potentially positive and negative active compounds, the levels of which can vary significantly even between batches of the same oils or extracts. Any product that has not been rigorously tested, especially natural products, should therefore be used with caution. The opportunity is to take the positive ingredients out of natural products, leaving the negative ones behind, to make an optimal formulation with a defined composition comprising only 'tried and tested' ingredients. The evidence base is still relatively small, and further research is required to help inform skincare practice and ultimately avoid fatal infections and prevent skin conditions such as AD from arising.

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KEY REFERENCES

2. Danby S, Cork MJ. The skin barrier in atopic dermatitis. In: Irvine AD, Hoeger PH, Yan A, editors. Textbook of pediatric dermatology. 3rd ed. Oxford: Blackwell; 2011.
13. Blume-Peytavi U, Hauser M, Stamatas GN, et al. Skin care practices for newborns and infants: review of the clinical evidence for best practices. *Pediatr Dermatol* 2012;29:1–14.
30. Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483–94.
52. Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). Evidence-based clinical practice guideline: neonatal skin care. Washington, DC: AWHONN; 2001.
53. Lund C, Kuller J, Lane A, et al. Neonatal skin care: the scientific basis for practice. *J Obstet Gynecol Neonatal Nurs* 1999;28:241–54.
69. Ananthapadmanabhan KP, Moore DJ, Subramanyan K, et al. Cleansing without compromise: the impact of cleansers on the skin barrier and the technology of mild cleansing. *Dermatol Therapy* 2004;17(Suppl. 1):16–25.
73. Lavender T, Bedwell C, Roberts SA, et al. Randomized, controlled trial evaluating a baby wash product on skin barrier function in healthy, term neonates. *J Obstet Gynecol Neonatal Nurs* 2013;42:203–14.
110. Darmstadt GL, Saha SK, Ahmed AS, et al. Effect of skin barrier therapy on neonatal mortality rates in preterm infants in Bangladesh: a randomized, controlled, clinical trial. *Pediatrics* 2008;121:522–9.
136. Lavender T, Furler C, Campbell M, et al. Effect on skin hydration of using baby wipes to clean the napkin area of newborn babies: assessor-blinded randomised controlled equivalence trial. *BMC Pediatr* 2012;12:59.
206. Blume-Peytavi U, Cork MJ, Faergemann J, et al. Bathing and cleansing in newborns from day 1 to first year of life: recommendations from a European round table meeting. *J Eur Acad Dermatol Venereol* 2009;23:751–9.

REFERENCES

- Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441–6.
- Danby S, Cork MJ. The skin barrier in atopic dermatitis. In: Irvine AD, Hoeger PH, Yan A, editors. *Textbook of pediatric dermatology*. 3rd ed. Oxford: Blackwell; 2011.
- Spergel JM, Paller AS. Atopic dermatitis and the atopic march. *J Allergy Clin Immunol* 2003;112:S118–27.
- Cork MJ, Danby SG, Vasilopoulos Y, et al. Epidermal barrier dysfunction in atopic dermatitis. *J Invest Dermatol* 2009;129:1892–908.
- Simpson EL, Chalmers JR, Hanifin J, et al. Barrier enhancement for eczema prevention—the BEEP feasibility study. 75th Annual Meeting of the Society-for-Investigative-Dermatology. Vol. 132. Raleigh, NC; 2012:S90.
- Evans NJ, Rutter N. Development of the epidermis in the newborn. *Biol Neonate* 1986;49:74–80.
- Rutter N. The immature skin. *Eur J Pediatr* 1996;155(Suppl. 2):S18–20.
- Chiou YB, Blume-Peytavi U. Stratum corneum maturation. A review of neonatal skin function. *Skin Pharmacol Physiol* 2004;17:57–66.
- Boralevi F, Hubiche T, Leaute-Labreze C, et al. Epicutaneous aeroallergen sensitization in atopic dermatitis infants – determining the role of epidermal barrier impairment. *Allergy* 2008;63:205–10.
- Brion L, Fleischman AR, Schwartz GJ. Evaluation of four length-weight formulas for estimating body surface area in newborn infants. *J Pediatr* 1985;107:801–3.
- Darmstadt GL, Dinulos JG. Neonatal skin care. *Pediatr Clin North Am* 2000;47:757–82.
- Kalia YN, Nonato LB, Lund CH, et al. Development of skin barrier function in premature infants. *J Invest Dermatol* 1998;111:320–6.
- Blume-Peytavi U, Hauser M, Stamatas GN, et al. Skin care practices for newborns and infants: review of the clinical evidence for best practices. *Pediatr Dermatol* 2012;29:1–14.
- Stamatas GN, Nikolovski J, Luedtke MA, et al. Infant skin microstructure assessed in vivo differs from adult skin in organization and at the cellular level. *Pediatr Dermatol* 2010;27(2):125–31.
- Nikolovski J, Stamatas GN, Kollias N, et al. Barrier function and water-holding and transport properties of infant stratum corneum are different from adult and continue to develop through the first year of life. *J Invest Dermatol* 2008;128:1728–36.
- Nakagawa N, Sakai S, Matsumoto M, et al. Relationship between NMF (lactate and potassium) content and the physical properties of the stratum corneum in healthy subjects. *J Invest Dermatol* 2004;122:755–63.
- Winge MC, Hoppe T, Berne B, et al. Filaggrin genotype determines functional and molecular alterations in skin of patients with atopic dermatitis and ichthyosis vulgaris. *PLoS ONE* 2011;6:e28254.
- Nemoto-Hasebe I, Akiyama M, Nomura T, et al. Clinical severity correlates with impaired barrier in filaggrin-related eczema. *J Invest Dermatol* 2009;129:682–9.
- Sergeant A, Campbell LE, Hull PR, et al. Heterozygous null alleles in filaggrin contribute to clinical dry skin in young adults and the elderly. *J Invest Dermatol* 2009;129:1042–5.
- Jungersted JM, Scheer H, Mempel M, et al. Stratum corneum lipids, skin barrier function and filaggrin mutations in patients with atopic eczema. *Allergy* 2010;65:911–18.
- Hachem JB, Crumrine D, Fluhr J, et al. pH directly regulates epidermal permeability barrier homeostasis, and stratum corneum integrity/cohesion. *J Invest Dermatol* 2003;121:345–53.
- Hachem JB, Man MQ, Crumrine D, et al. Sustained serine proteases activity by prolonged increase in pH leads to degradation of lipid processing enzymes and profound alterations of barrier function and stratum corneum integrity. *J Invest Dermatol* 2005;125:510–20.
- Ramaswamy P, Downing DT, Pochi PE, et al. Chemical composition of human skin surface lipids from birth to puberty. *J Invest Dermatol* 1970;54:139–44.
- Wertz PW, Downing DT. Linoleate content of epidermal acylglucosylceramide in newborn, growing and mature mice. *Biochim Biophys Acta* 1986;876:469–73.
- Drake DR, Brogden KA, Dawson DV, et al. Thematic review series: skin lipids. Antimicrobial lipids at the skin surface. *J Lipid Res* 2008;49:4–11.
- West DP, Halket JM, Harvey DR, et al. Percutaneous absorption in preterm infants. *Pediatr Dermatol* 1987;4:234–7.
- Basta M, Wilburg J, Heczko PB. In vitro effects of skin lipid extracts on skin bacteria in relation to age and acne changes. *J Invest Dermatol* 1980;74:437–9.
- Shaw TE, Currie GP, Koudelka CW, et al. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2011;131:67–73.
- Odhiambo JA, Williams HC, Clayton TO, et al. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009;124:1251–8 e23.
- Bieber T. Atopic dermatitis. *N Engl J Med* 2008;358:1483–94.
- Illi S, von Mutius E, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004;113:925–31.
- Cork MJ, Danby S, Vasilopoulos Y, et al. Gene-environment interactions in atopic dermatitis. *Drug Discov Today: Dis Mech* 2008;5:e11–31.
- Brown SJ, McLean WH. Eczema genetics: current state of knowledge and future goals. *J Invest Dermatol* 2009;129:543–52.
- Fluhr J, Bankova LG. Skin surface pH: Mechanism, measurement, importance. In: Serup J, Jemec GB, Grove GL, editors. *Handbook of non-invasive methods and the skin*. Boca Raton: CRC Press; 2006. p. 411–20.
- Ewence A, Rumsby P, Danby S, et al. A review of skin irritation and tap water quality. Swindon: WRc; 2011.
- Warren R, Ertel KD, Bartolo RG, et al. The influence of hard water (calcium) and surfactants on irritant contact dermatitis. *Contact Dermatol* 1996;35:337–43.
- Lee SH, Elias PM, Proksch E, et al. Calcium and potassium are important regulators of barrier homeostasis in murine epidermis. *J Clin Invest* 1992;89:530–8.
- McNally NJ, Williams HC, Phillips DR, et al. Atopic eczema and domestic water hardness. *Lancet* 1998;352:527–31.
- Miyake Y, Yokoyama T, Yura A, et al. Ecological association of water hardness with prevalence of childhood atopic dermatitis in a Japanese urban area. *Environ Res* 2004;94:33–7.
- Thomas KS, Sach TH. A multicentre randomized controlled trial of ion-exchange water softeners for the treatment of eczema in children: protocol for the Softened Water Eczema Trial (SWET). *Br J Dermatol* 2008;159:561–6.
- Darsow U, Wollenberg A, Simon D, et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol* 2009;24:317–28.
- Lewis-Jones S, Cork MJ, Clark C, et al. Atopic eczema in children – Guideline consultation: A systematic review of the treatments for atopic eczema and guideline for its management. London: NICE, Department of Health; 2007.
- Paller AS, Mancini A. *Hurwitz clinical pediatric dermatology*. 3rd ed. Philadelphia: Saunders; 2006.
- Siqueira WL, Bermejo PR, Mustacchi Z, et al. Buffer capacity, pH, and flow rate in saliva of children aged 2–60 months with Down syndrome. *Clin Oral Investig* 2005;9:26–9.
- Harrison VC, Peat G. Significance of milk pH in newborn infants. *BMJ* 1972;4:515–18.
- Ireson NJ, Tait JS, MacGregor GA, et al. Comparison of nasal pH values in black and white individuals with normal and high blood pressure. *Clin Sci* 2001;100:327–33.
- Adam R. Skin care of the diaper area. *Pediatr Dermatol* 2008;25:427–33.
- Lack G, Fox D, Northstone K, et al. Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003;348:977–85.
- Gelmetti C. Skin cleansing in children. *J Eur Acad Dermatol Venereol* 2001;15(Suppl. 1):12–15.
- Peters KL. Bathing premature infants: physiological and behavioral consequences. *Am J Crit Care* 1998;7:90–100.
- Henningsson A, Nystrom B, Tunnell R. Bathing or washing babies after birth? *Lancet* 1981;2:1401–3.
- Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). Evidence-based clinical practice guideline: neonatal skin care. Washington, DC: AWHONN; 2001.
- Lund C, Kuller J, Lane A, et al. Neonatal skin care: the scientific basis for practice. *J Obstet Gynecol Neonatal Nurs* 1999;28:241–54.
- Als H, Lawhon G, Brown E, et al. Individualized behavioral and environmental care for the very low birth weight preterm infant at high risk for bronchopulmonary dysplasia: neonatal intensive care unit and developmental outcome. *Pediatrics* 1986;78:1123–32.
- Kanda K, Tochihara Y, Ohnaka T. Bathing before sleep in the young and in the elderly. *Eur J Appl Physiol Occup Physiol* 1999;80:71–5.
- Nako Y, Harigaya A, Tomomasa T, et al. Effects of bathing immediately after birth on early neonatal adaptation and morbidity: a prospective randomized comparative study. *Pediatr Int* 2000;42:517–22.
- Mirowski GW, Frieden IJ, Miller C. Iatrogenic scald burn: a consequence of institutional

- infection control measures. *Pediatrics* 1996;98:963–5.
58. Joglekar VM. Barrier properties of vernix caseosa. *Arch Dis Child* 1980;55:817–19.
 59. Hoath SB. The stickiness of newborn skin: bioadhesion and the epidermal barrier. *J Pediatr* 1997;131:338–40.
 60. Tollin M, Bergsson G, Kai-Larsen Y, et al. Vernix caseosa as a multi-component defence system based on polypeptides, lipids and their interactions. *Cell Mol Life Sci* 2005;62:2390–9.
 61. Yoshio H, Tollin M, Gudmundsson GH, et al. Antimicrobial polypeptides of human vernix caseosa and amniotic fluid: implications for newborn innate defense. *Pediatr Res* 2003;53:211–16.
 62. Camm J. Skincare for newborns: guidelines and advice. *RCM Midwives* 2006;9:126.
 63. Drennan VG, Goodman C. *Oxford handbook of primary care and community nursing*. Oxford: Oxford University Press; 2007.
 64. Hughes K. Advocating good practice in skin protection. *Br J Midwifery* 2011;19:773–5.
 65. Garcia Bartels N, Mieczko A, Schink, T, et al. Influence of bathing or washing on skin barrier function in newborns during the first four weeks of life. *Skin Pharmacol Physiol* 2009;22(5):248–57.
 66. Lavender T, Bedwell C, Tsekiri-O'Brien E, et al. A qualitative study exploring women's and health professional's views of newborn bathing practices. *Evid base Midwifery* 2009;7:112–21.
 67. Gfatter R, Hackl P, Braun F. Effects of soap and detergents on skin surface pH, stratum corneum hydration and fat content in infants. *Dermatology* 1997;195:258–62.
 68. Tsai TF, Maibach HI. How irritant is water? An overview. *Contact Dermatitis* 1999;41:311–14.
 69. Ananthapadmanabhan KP, Moore DJ, Subramanyan K, et al. Cleansing without compromise: the impact of cleansers on the skin barrier and the technology of mild cleansing. *Dermatol Therapy* 2004;17(Suppl. 1):16–25.
 70. Crozier K, Macdonald S. Effective skin-care regimes for term newborn infants: a structured literature review. *Evid base Midwifery* 2010;8:128–35.
 71. Garcia Bartels N, Scheufele R, Prosch F, et al. Effect of standardized skin care regimens on neonatal skin barrier function in different body areas. *Pediatr Dermatol* 2010;27:1–8.
 72. Dizon MV, Galzote C, Estandislo R, et al. Tolerance of baby cleansers in infants: a randomized controlled trial. *Indian Pediatr* 2010;47:959–63.
 73. Lavender T, Bedwell C, Roberts SA, et al. Randomized, controlled trial evaluating a baby wash product on skin barrier function in healthy, term neonates. *J Obstet Gynecol Neonatal Nurs* 2013;42:203–14.
 74. Simon NP, Simon MW. Changes in newborn bathing practices may increase the risk for omphalitis. *Clin Pediatr (Phila)* 2004;43:763–7.
 75. Archer GL. Alteration of cutaneous staphylococcal flora as a consequence of antimicrobial prophylaxis. *Rev Infect Dis* 1991;13(Suppl. 10):S805–9.
 76. Chen YE, Tsao H. The skin microbiome: Current perspectives and future challenges. *J Am Acad Dermatol* 2013;69:143–55.
 77. Janniger CK, Bryngil JM. Hair in infancy and childhood. *Cutis* 1993;51:336–8.
 78. Walters RM, Fevola MJ, LiBrizzi JJ, et al. Designing cleansers for the unique needs of baby skin. *Cosm Toil* 2008;123:53–60.
 79. Bree A, Siegfried EC. General principles of skin care in children. In: Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 3rd ed. Philadelphia: Elsevier Health Sciences; 2003. p. 93.
 80. Lin RL, Tinkle LL, Janniger CK. Skin care of the healthy newborn. *Cutis* 2005;75:25–30.
 81. Danby S, Cork MJ. Current and future trends: skin diseases and treatment. In: Benson HA, Watkinson A, editors. *Transdermal and topical drug delivery: principles and practice*. John Wiley & Sons; 2011.
 82. Rawlings AV, Lombard KJ. A review on the extensive skin benefits of mineral oil. *Int J Cosm Sci* 2012;34:511–18.
 83. Patzelt A, Lademann J, Richter H, et al. In vivo investigations on the penetration of various oils and their influence on the skin barrier. *Skin Res Technol* 2012;18:364–9.
 84. Danby S, Al Enezi T, Sultan A, et al. The effect of Aqueous Cream BP on the skin barrier in volunteers with a previous history of atopic dermatitis. *Br J Dermatol* 2011;165:329–34.
 85. Mohammed D, Matts PJ, Hadgraft J, et al. Influence of Aqueous Cream BP on corneocyte size, maturity, skin protease activity, protein content and transepidermal water loss. *Br J Dermatol* 2011;164:1304–10.
 86. Tsang M, Guy RH. Effect of Aqueous Cream BP on human stratum corneum in vivo. *Br J Dermatol* 2010;163:954–8.
 87. Cork MJ, Timmins J, Holden C, et al. An audit of adverse drug reactions to aqueous cream in children with atopic eczema. *Pharm J* 2003;271:746–7.
 88. Brown K, Higgs-Bayliss T, Chittock J, et al. The effect of an emollient cream containing 5% urea on the biophysical properties of aged skin. 11th meeting of the European Epidermal Barrier Research Network, Edinburgh, 2013.
 89. Rawlings AV, Canestrari DA, Dobkowski B. Moisturizer technology versus clinical performance. *Dermatol Therapy* 2004;17(Suppl. 1):49–56.
 90. Wren K, Nohlgard C, Nyberg F, et al. Treatment with a barrier-strengthening moisturizing cream delays relapse of atopic dermatitis: a prospective and randomized controlled clinical trial. *J Eur Acad Dermatol Venereol* 2009;23:1267–72.
 91. Loden M. Effect of moisturizers on epidermal barrier function. *Clin Dermatol* 2012;30:286–96.
 92. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000;4:1–191.
 93. Simpson EL, Berry TM, Brown PA, et al. A pilot study of emollient therapy for the primary prevention of atopic dermatitis. *J Am Acad Dermatol* 2010;63:587–93.
 94. Williams HC, Chalmers JR, Simpson EL. Prevention of atopic dermatitis. *F1000 Med Rep* 2012;4:24.
 95. Beyer K, Strauss L. Infant massage programs may assist in decreasing parental perceived stress levels in new parents. *Occup Ther* 2002;16:53–68.
 96. Cheng CD, Volk AA, Marini ZA. Supporting fathering through infant massage. *J Perinat Educ* 2011;20:200–9.
 97. Modrcin-Talbott MA, Harrison LL, Groer MW, et al. The biobehavioral effects of gentle human touch on preterm infants. *Nurs Sci Q* 2003;16:60–7.
 98. Vickers A, Ohlsson A, Lacy JB, et al. Massage for promoting growth and development of preterm and/or low birth-weight infants. *Cochrane Database Syst Rev* 2004;(2):CD000390.
 99. Bohles H, Bieber MA, Heird WC. Reversal of experimental essential fatty acid deficiency by cutaneous administration of safflower oil. *Am J Clin Nutr* 1976;29:398–401.
 100. Hunt CE, Engel RR, Modler S, et al. Essential fatty acid deficiency in neonates: inability to reverse deficiency by topical applications of EFA-rich oil. *J Pediatr* 1978;92:603–7.
 101. Sankaranarayanan K, Mondkar JA, Chauhan MM, et al. Oil massage in neonates: an open randomized controlled study of coconut versus mineral oil. *Indian Pediatr* 2005;42:877–84.
 102. Solanki K, Matnani M, Kale M, et al. Transcutaneous absorption of topically massaged oil in neonates. *Indian Pediatr* 2005;42:998–1005.
 103. Agero AL, Verallo-Rowell VM. A randomized double-blind controlled trial comparing extra virgin coconut oil with mineral oil as a moisturizer for mild to moderate xerosis. *Dermatitis* 2004;15:109–16.
 104. Darmstadt GL, Badrawi N, Law PA, et al. Topically applied sunflower seed oil prevents invasive bacterial infections in preterm infants in Egypt: a randomized, controlled clinical trial. *Pediatr Infect Dis J* 2004;23:719–25.
 105. Darmstadt GL, Saha SK, Ahmed AS, et al. Effect of topical treatment with skin barrier-enhancing emollients on nosocomial infections in preterm infants in Bangladesh: a randomised controlled trial. *Lancet* 2005;365:1039–45.
 106. Verallo-Rowell VM, Dillague KM, Syah-Tjundawan BS. Novel antibacterial and emollient effects of coconut and virgin olive oils in adult atopic dermatitis. *Dermatitis* 2008;19:308–15.
 107. Lucas L, Russell A, Keast R. Molecular mechanisms of inflammation. Anti-inflammatory benefits of virgin olive oil and the phenolic compound oleocanthal. *Curr Pharm Des* 2011;17:754–68.
 108. Intaphuak S, Khonsung P, Panthong A. Anti-inflammatory, analgesic, and antipyretic activities of virgin coconut oil. *Pharm Biol* 2010;48:151–7.
 109. Loden M, Andersson AC. Effect of topically applied lipids on surfactant-irritated skin. *Br J Dermatol* 1996;134:215–20.
 110. Darmstadt GL, Saha SK, Ahmed AS, et al. Effect of skin barrier therapy on neonatal mortality rates in preterm infants in Bangladesh: a randomized, controlled, clinical trial. *Pediatrics* 2008;121:522–9.
 111. Vaivre-Douret L, Oriot D, Blossier P, et al. The effect of multimodal stimulation and cutaneous application of vegetable oils on neonatal development in preterm infants: a randomized controlled trial. *Child Care Health Dev* 2009;35:96–105.
 112. Darmstadt GL, Mao-Qiang M, Chi E, et al. Impact of topical oils on the skin barrier: possible implications for neonatal health in developing countries. *Acta Paediatr* 2002;91:546–54.
 113. Danby S, Al Enezi T, Lavender T, et al. Effect of olive and sunflower seed oil on the adult skin barrier: implications for neonatal skin care. *Pediatr Dermatol* 2012;1–9.

114. Kranke B, Komericki P, Aberer W. Olive oil – contact sensitizer or irritant? *Contact Dermatitis* 1997;36:5–10.
115. Schliemann-Willers S, Wigger-Alberti W, Kleesz P, et al. Natural vegetable fats in the prevention of irritant contact dermatitis. *Contact Dermatitis* 2002;46:6–12.
116. Tanojo H, Junginger HE, Boddé HE. In vivo human skin permeability enhancement by oleic acid: transepidermal water loss and Fourier-transform infrared spectroscopy studies. *J Control Release* 1997;47:31–9.
117. Agarwal KN, Gupta A, Pushkarna R, et al. Effects of massage and use of oil on growth, blood flow and sleep pattern in infants. *Indian J Med Res* 2000;112:212–17.
118. Darmstadt GL, Saha SK. Traditional practice of oil massage of neonates in Bangladesh. *J Health Popul Nutr* 2002;20:184–8.
119. Fernandez A, Patkar S, Chawla C, et al. Oil application in preterm babies – a source of warmth and nutrition. *Indian Pediatr* 1987;24:1111–16.
120. Mullany LC, Darmstadt GL, Khatri SK, et al. Traditional massage of newborns in Nepal: implications for trials of improved practice. *J Trop Pediatr* 2005;51:82–6.
121. Yurdakok M, Yurdakok K. Topical vegetable oil therapy for premature infants. *J Pediatr* 1997;130:330–2.
122. Cooke A, Cork MJ, Danby S, et al. A national survey of UK maternity and neonatal units regarding the use of oil for baby skincare. *Br J Midwifery* 2011.
123. Beukers SM, Rustemeyer T, Bruynzeel DP. Cheilitis due to olive oil. *Contact Dermatitis* 2008;59:253–5.
124. Barada JH. Pseudoanuria due to superabsorbent diapers. *N Engl J Med* 1991;325:892–3.
125. Hermansen MC, Buches M. Urine output determination from superabsorbent and regular diapers under radiant heat. *Pediatrics* 1988;81:428–31.
126. Visscher MO, Chatterjee R, Munson KA, et al. Development of diaper rash in the newborn. *Pediatr Dermatol* 2000;17:52–7.
127. Kazaks EL, Lane AT. Diaper dermatitis. *Pediatr Clin North Am* 2000;47:909–19.
128. Berg RW, Buckingham KW, Stewart RL. Etiologic factors in diaper dermatitis: the role of urine. *Pediatr Dermatol* 1986;3:102–6.
129. Ferrazzini G, Kaiser RR, Hirsig Cheng SK, et al. Microbiological aspects of diaper dermatitis. *Dermatology* 2003;206:136–41.
130. Buckingham KW, Berg RW. Etiologic factors in diaper dermatitis: the role of feces. *Pediatr Dermatol* 1986;3:107–12.
131. Lane AT, Rehder PA, Helm K. Evaluations of diapers containing absorbent gelling material with conventional disposable diapers in newborn infants. *Am J Dis Child* 1990;144:315–18.
132. Odio M, Friedlander SF. Diaper dermatitis and advances in diaper technology. *Curr Opin Pediatr* 2000;12:342–6.
133. Wong DL, Brantly D, Clutter LB, et al. Diapering choices: a critical review of the issues. *Pediatr Nurs* 1992;18:41–54.
134. Odio M, Streicher-Scott J, Hansen RC. Disposable baby wipes: efficacy and skin mildness. *Dermatol Nurs* 2001;13:107–12, 17–18, 21.
135. Timmermans A, De Hertog S, Gladys K, et al. 'Dermatologically tested' baby toilet tissues: a cause of allergic contact dermatitis in adults. *Contact Dermatitis* 2007;57:97–9.
136. Lavender T, Furber C, Campbell M, et al. Effect on skin hydration of using baby wipes to clean the napkin area of newborn babies: assessor-blinded randomised controlled equivalence trial. *BMC Pediatr* 2012;12:59.
137. Fields KS, Nelson T, Powell D. Contact dermatitis caused by baby wipes. *J Am Acad Dermatol* 2006;54: S230–2.
138. Zoli V, Tosti A, Silvani S, et al. Moist toilet papers as possible sensitizers: review of the literature and evaluation of commercial products in Italy. *Contact Dermatitis* 2006;55: 252–4.
139. Adam R, Schnetz B, Mathey P, et al. Clinical demonstration of skin mildness and suitability for sensitive infant skin of a new baby wipe. *Pediatr Dermatol* 2009;26:506–13.
140. Garcia-Bartels N, Massoudy L, Schink T, et al. Use of baby wipes in the diaper area in newborns: a prospective, randomized clinical study on skin barrier. Second Congress of the European Academy of Paediatrics; Poster sessions. *Arch Dis Child* 2008;93:222.
141. Mancini AJ. Skin. *Pediatrics* 2004;113: 1114–19.
142. Brannan DK, Dille JC. Type of closure prevents microbial contamination of cosmetics during consumer use. *Appl Environ Microbiol* 1990;56:1476–9.
143. Carr J, Akram M, Sultan A, et al. Contamination of emollient creams and ointments with *Staphylococcus aureus* – in children with atopic eczema. 5th George Rajka International Symposium on Atopic Dermatitis, Kyoto, 2008.
144. Sultan A, Carr J, Danby S, et al. A case of life-threatening infections due to preservative absence in a topical cream and audit demonstrating magnitude of the problem. 26th International Congress of Pediatrics of the International Pediatrics Association, South Africa, 2010.
145. Alvarez-Lerma F, Maull E, Terradas R, et al. Moisturizing body milk as a reservoir of *Burkholderia cepacia*: outbreak of nosocomial infection in a multidisciplinary intensive care unit. *Crit Care* 2008;12:R10.
146. Dore S, Buchan D, Coulas S, et al. Alcohol versus natural drying for newborn cord care. *J Obstet Gynecol Neonatal Nurs* 1998;27: 621–7.
147. Evens K, George J, Angst D, et al. Does umbilical cord care in preterm infants influence cord bacterial colonization or detachment? *J Perinatol* 2004;24:100–4.
148. Janssen PA, Selwood BL, Dobson SR, et al. To dye or not to dye: a randomized, clinical trial of a triple dye/alcohol regime versus dry cord care. *Pediatrics* 2003;111:15–20.
149. Medves JM, O'Brien BA. Cleaning solutions and bacterial colonization in promoting healing and early separation of the umbilical cord in healthy newborns. *Can J Public Health* 1997;88:380–2.
150. Belfrage E, Enocksson E, Kalin M, et al. Comparative efficiency of chlorhexidine and ethanol in umbilical cord care. *Scand J Infect Dis* 1985;17:413–20.
151. Verber IG, Pagan FS. What cord care – if any? *Arch Dis Child* 1993;68:594–6.
152. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Developmental pharmacology – drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003;349:1157–67.
153. West DP, Worobec S, Solomon LM. Pharmacology and toxicology of infant skin. *J Invest Dermatol* 1981;76:147–50.
154. Blumer JL. The therapeutic orphan – 30 years later. Joint conference of the Pediatric Pharmacology Research Unit Network, the European Society of Developmental Pharmacology, and the National Institute of Child Health and Human Development, Washington, DC. *Pediatrics* 1997;104:581–645.
155. Rutter N. Percutaneous drug absorption in the newborn: hazards and uses. *Clin Perinatol* 1987;14:911–30.
156. Cooke JV. Dermatitis of the diaper region in infants (Jacquet dermatitis). *Arch Dermatol Syphilol* 1926;14:539–46.
157. Micali G, Lacarrubba F, Bongu A, et al. The skin barrier. In: Freinkel RK, Woodley DT, editors. *The biology of the skin*. New York: Taylor & Francis; 2001. p. 219–31.
158. Becks VE, Lorenzoni NM. *Pseudomonas aeruginosa* outbreak in a neonatal intensive care unit: a possible link to contaminated hand lotion. *Am J Infect Control* 1995;23:396–8.
159. Brannan DK, Dille JC, Kaufman DJ. Correlation of in vitro challenge testing with consumer use testing for cosmetic products. *Appl Environ Microbiol* 1987;53:1827–32.
160. Madani TA, Alsaedi S, James L, et al. *Serratia marcescens*-contaminated baby shampoo causing an outbreak among newborns at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. *J Hosp Infect* 2011;78:16–19.
161. Na'was T, Alkofahi A. Microbial contamination and preservative efficacy of topical creams. *J Clin Pharm Ther* 1994;19:41–6.
162. Ravita TD, Tanner RS, Ahearn DG, et al. Post-consumer use efficacies of preservatives in personal care and topical drug products: relationship to preservative category. *J Ind Microbiol Biotechnol* 2009;36:35–8.
163. Sartor C, Jacomo V, Duvivier C, et al. Nosocomial *Serratia marcescens* infections associated with extrinsic contamination of a liquid non-medicated soap. *Infect Control Hosp Epidemiol* 2000;21:196–9.
164. Smales O. A comparison of umbilical cord treatment in the control of superficial infection. *N Z Med J* 1988;101:453–5.
165. Andrich MP, Golden SM. Umbilical cord care. A study of bacitracin ointment vs. triple dye. *Clin Pediatr (Phila)* 1984;23:342–4.
166. Wald ER, Snyder MJ, Gutberlet RL. Group B beta-hemolytic streptococcal colonization. Acquisition, persistence, and effect of umbilical cord treatment with triple dye. *Am J Dis Child* 1977;131:178–80.
167. Paes B, Jones CC. An audit of the effect of two cord-care regimens on bacterial colonization in newborn infants. *Qual Rev Bull* 1987;13: 109–13.
168. Speck WT, Driscoll JM, O'Neil J, et al. Effect of antiseptic cord care on bacterial colonization in the newborn infant. *Chemotherapy* 1980;26:372–6.
169. Garland JS, Buck RK, Maloney P, et al. Comparison of 10% povidone-iodine and 0.5% chlorhexidine gluconate for the prevention of peripheral intravenous catheter colonization in neonates: a prospective trial. *Pediatr Infect Dis J* 1995;14:510–16.
170. Garland JS, Alex CP, Mueller CD, et al. Local reactions to a chlorhexidine gluconate-impregnated antimicrobial dressing in very low birth weight infants. *Pediatr Infect Dis J* 1996;15:912–14.
171. Aggett PJ, Cooper LV, Ellis SH, et al. Percutaneous absorption of chlorhexidine in neonatal cord care. *Arch Dis Child* 1981;56:878–80.

172. Pyati SP, Ramamurthy RS, Krauss MT, et al. Absorption of iodine in the neonate following topical use of povidone iodine. *J Pediatr* 1977;91:825–8.
173. Barakat M, Carson D, Hetherington AM, et al. Hypothyroidism secondary to topical iodine treatment in infants with spina bifida. *Acta Paediatr* 1994;83:741–3.
174. Harpin V, Rutter N. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1982;57:477–9.
175. Howard R. The appropriate use of topical antimicrobials and antiseptics in children. *Pediatr Ann* 2001;30:219–24.
176. Dalt LD, Dall'Amico R, Laverda AM, et al. Percutaneous ethyl alcohol intoxication in a one-month-old infant. *Pediatr Emerg Care* 1991;7:343–4.
177. Maki DG, Ringer M, Alvarado CJ. Prospective randomised trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet* 1991;338:339–43.
178. Light IJ, Sutherland JM. Effect of topical antibacterial agents on the acquisition of bacteria by newborn infants. *Antimicrob Agents Chemother* (Bethesda) 1968;8:274–8.
179. Davies J, Babb JR, Ayliffe GA. The effect on the skin flora of bathing with antiseptic solutions. *J Antimicrob Chemother* 1977;3:473–81.
180. Micromedex. Poisindex®. Truven Health Analytics; 2013.
181. Lund CH, Kuller J, Lane AT, et al. Neonatal skin care: evaluation of the AWHONN/NANN research-based practice project on knowledge and skin care practices. Association of Women's Health, Obstetric and Neonatal Nurses/ National Association of Neonatal Nurses. *J Obstet Gynecol Neonatal Nurs* 2001;30:30–40.
182. Sedin G, Hammarlund K, Nilsson GE, et al. Measurements of transepidermal water loss in newborn infants. *Clin Perinatol* 1985;12:79–99.
183. Hammarlund K, Nilsson GE, Oberg PA, et al. Transepidermal water loss in newborn infants I. Relation to ambient humidity and site of measurement and estimation of total transepidermal water loss. *Acta Paediatr* 1977;66:553–62.
184. Kjartansson S, Arsan S, Hammarlund K, et al. Water loss from the skin of term and preterm infants nursed under a radiant heater. *Pediatr Res* 1995;37:233–8.
185. Bertini G, Perugi S, Elia S, et al. Transepidermal water loss and cerebral hemodynamics in preterm infants: conventional versus LED phototherapy. *Eur J Pediatr* 2008;167:37–42.
186. Agren J, Sjors G, Sedin G. Ambient humidity influences the rate of skin barrier maturation in extremely preterm infants. *Journal Pediatr* 2006;148:613–17.
187. Harpin VA, Rutter N. Humidification of incubators. *Arch Dis Child* 1985;60:219–24.
188. Knauth A, Gordin M, McNelis W, et al. Semipermeable polyurethane membrane as an artificial skin for the premature neonate. *Pediatrics* 1989;83:945–50.
189. Vernon HJ, Lane AT, Wischerath LJ, et al. Semipermeable dressing and transepidermal water loss in premature infants. *Pediatrics* 1990;86:357–62.
190. Donahue ML, Phelps DL, Richter SE, et al. A semipermeable skin dressing for extremely low birth weight infants. *J Perinatol* 1996;16:20–6.
191. Bhandari V, Brodsky N, Porat R. Improved outcome of extremely low birth weight infants with Tegaderm application to skin. *J Perinatol* 2005;25:276–81.
192. Baumgart S. Reduction of oxygen consumption, insensible water loss, and radiant heat demand with use of a plastic blanket for low-birth-weight infants under radiant warmers. *Pediatrics* 1984;74:1022–8.
193. Kiechl-Kohlendorfer U, Berger C, Inzinger R. The effect of daily treatment with an olive oil/lanolin emollient on skin integrity in preterm infants: a randomized controlled trial. *Pediatr Dermatol* 2008;25:174–8.
194. Beeram M, Olvera R, Krauss D, et al. Effects of topical emollient therapy on infants at or less than 27 weeks' gestation. *J Natl Med Assoc* 2006;98:261–4.
195. Lane AT, Drost SS. Effects of repeated application of emollient cream to premature neonates' skin. *Pediatrics* 1993;92:415–19.
196. Nopper AJ, Horii KA, Sookdeo-Drost S, et al. Topical ointment therapy benefits premature infants. *J Pediatr* 1996;128:660–9.
197. Conner JM, Soll RF, Edwards WH. Topical ointment for preventing infection in preterm infants. *Cochrane Database Syst Rev* 2004;(1):CD001150.
198. Darmstadt GL, Saha SK, Ahmed AS, et al. Effect of topical emollient treatment of preterm neonates in Bangladesh on invasion of pathogens into the bloodstream. *Pediatr Res* 2007;61:588–93.
199. Siegfried EC. Neonatal skin and skin care. *Dermatol Clin* 1998;16:437–46.
200. Baker SE, Smith BJ, Donohue PK, et al. Skin care management practices for premature infants. *J Perinatol* 1999;19:426–31.
201. Munson KA, Bare DE, Hoath SB, et al. A survey of skin care practices for premature low birth weight infants. *Neonatal Netw* 1999;18:25–31.
202. Siegfried EC, Shah PY. Skin care practices in the neonatal nursery: a clinical survey. *J Perinatol* 1999;19:31–9.
203. Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). Neonatal skin care; evidence based clinical guidelines. In: NICE, Postnatal Care Guidelines (Health, NCCfWsaCs). 2nd ed. London: National Institute of Health and Clinical Excellence; 2007.
204. Lund CH, Osborne JW. Validity and reliability of the neonatal skin condition score. *J Obstet Gynecol Neonatal Nurs* 2004;33:320–7.
205. WHO. Pregnancy, childbirth, postpartum and newborn care: A guide for essential practice. Geneva: World Health Organization; 2006.
206. Blume-Peytavi U, Cork MJ, Faergemann J, et al. Bathing and cleansing in newborns from day 1 to first year of life: recommendations from a European round table meeting. *J Eur Acad Dermatol Venereol* 2009;23:751–9.
207. Demott K, Bick D, Norman R, et al. Clinical guidelines and evidence review for post natal care: routine post natal care of recently delivered women and their babies. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2006.
208. Darmstadt GL, Black RE, Santosham M. Research priorities and postpartum care strategies for the prevention and optimal management of neonatal infections in less developed countries. *Pediatr Infect Dis J* 2000;19:739–50.
209. Eichenfield LF, McCollum A, Msika P. The benefits of sunflower oleodistillate (SOD) in pediatric dermatology. *Pediatr Dermatol* 2009;26:669–75.

Diagnostic and Therapeutic Procedures

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Introduction

Diagnostic and therapeutic procedures are a standard part of the evaluation and management of dermatologic conditions in neonates and infants. Performing procedures on younger children can be technically challenging, and requires knowledge of differences in approach and other special considerations due to the child's young age. This chapter discusses the most common of these diagnostic and therapeutic procedures.

Diagnostic procedures

BACTERIAL CULTURE

Bacterial culture is a frequently performed diagnostic test. Purulent material draining from a pustule or nodule can easily be obtained with a bacterial swab. If the material is dry or crusted, wetting the swab with water prior to rubbing the area increases the likelihood of obtaining material to grow an organism. The results of a Gram stain performed by the microbiology laboratory are usually available within a few hours, while the final bacterial culture result with drug susceptibilities may not be known for 48–72 h. The laboratory should be notified when Gram-negative or anaerobic bacterial infections are suspected, so that specific culture media may be used.

Bacteria causing certain infections such as necrotizing fasciitis may not be easily cultured from superficial skin samples, so that a skin biopsy for frozen section may be necessary for a rapid diagnosis (see 'Skin biopsy', below). A bacterial stain such as Brown–Brenn performed on the histologic sections can differentiate Gram-positive from Gram-negative organisms.

KOH PREPARATION

Potassium hydroxide (KOH) preparations are useful to identify the presence of fungi and yeast. They can be performed on samples of skin, hair, and nails. The skin should be scraped such that adequate material is available for microscopic examination (Box 6.1). If the KOH preparation is negative or equivocal, the skin scales may be placed onto fungal culture plates or sent for culture in an appropriate container, such as a sterile urine cup or wax paper envelope (see 'Fungal culture', below).

A scalp sample may be obtained by wetting a cotton-tipped applicator with water and rubbing the suspected area of involvement.¹ Another technique is to use a toothbrush² or gynecologic viral collection brush.³ The material from the swab is plated directly onto the fungal culture plate. Hairs can be plucked for culture, but this is not usually recommended in infants because of the pain caused by pulling hairs. Usually enough hairs can be gathered by scraping the scalp with a glass slide or #15 blade.

For nail samples, a sharp instrument, such as a Skeele curette, is used to collect debris from underneath the nail plate and this material can be stabbed directly onto the fungal plate. Nail clippings can be obtained by using a nail nipper. In young infants with soft nails, a cuticle nipper is sometimes sharp enough. The clippings can either be placed directly on the culture medium or in a sterile cup for the laboratory to plate. In addition, nail clippings can be placed in formalin and sent directly to pathology so that a periodic acid Schiff (PAS) stain⁴ can be performed; the results are usually known within 2–3 days compared with 30 days, which is the standard for fungal cultures in a microbiology laboratory. This method has been shown to be more reliable than KOH preparation and fungal culture in detecting the presence of organisms; however, fungal culture remains the gold standard for identifying the organism and determining drug susceptibilities.⁴

FUNGAL CULTURE

Mycosel™ agar and mycobiotic agar are two types of fungal culture media that are frequently used. They contain Sabouraud dextrose agar with chloramphenicol and cycloheximide to decrease bacterial overgrowth.

For deep fungal infections of the skin, a skin biopsy is necessary so that material from the dermis, and sometimes the subcutaneous fat, can be cultured, since the organism is not present in the superficial epidermal scales (see 'Skin biopsy', below).

DIRECT FLUORESCENT ANTIBODY TEST FOR DIAGNOSIS OF HERPES VIRUS INFECTION

Direct fluorescent antibody (DFA) testing uses mouse monoclonal antibodies to detect herpes viruses such as herpes simplex virus (HSV) 1 and 2 and varicella-zoster virus (VZV).⁵ Specimens are best obtained from the base of a ruptured vesicle, erosion, or ulcer. The likelihood of a positive result is much lower if the lesions are crusted or already healing. A Dacron® swab with a plastic shaft is used to rub the lesion and the swab is placed in viral transport medium. A calcium alginate swab should not be used because the chemicals are toxic to the virus. The laboratory can prepare the slide after cytopsin preparation; however, a slide can also be prepared at the bedside by careful rubbing of the swab onto the slide, which is allowed to air dry prior to transport to the laboratory.

VIRAL CULTURE

Using a Dacron® tipped swab, the fluid from an intact vesicle is absorbed and the swab is rubbed over the base of the lesion

BOX 6.1 TECHNIQUE: KOH PREPARATION

1. Scrape the skin with the edge of a glass microscopic slide, a #15 blade, or a double-edged knife (Joseph or Fomon blade).
2. Spread the skin scales on a glass microscopic slide.
3. Apply 1–2 drops of 10–20% KOH solution prior to placement of the coverslip or place the coverslip first and apply 1–2 drops at the edge, allowing the liquid to flow beneath the coverslip. A KOH solution that also contains DMSO (dimethyl sulfoxide) dissolves the keratin more rapidly, leaving fungal elements undisturbed.
4. Press the coverslip to disrupt the keratinocytes and wait 10–20 min to allow the KOH to dissolve the keratin, leaving the hyphae behind.

prior to placement in viral transport medium (buffered isotonic saline solution, often with antibiotics added to prevent bacterial contamination). The results are usually available in 2–3 days for herpes simplex viruses and 7–14 days for varicella-zoster virus.

Viral culture has historically been the gold standard for isolating viral pathogens, such as herpes viruses; however, this is likely to change with improved polymerase chain reaction (PCR) techniques.⁶

POLYMERASE CHAIN REACTION (PCR) TEST FOR DIAGNOSIS OF HERPES VIRUS INFECTION

Polymerase chain reaction (PCR) is now used by many laboratories to definitively identify herpes virus infections as well as other viral infections. Compared with viral culture, this test is more sensitive and the result is available more rapidly.⁷ The swab obtained for viral culture that has been placed in viral transport medium can be used for PCR.⁸

SCABIES PREPARATION

Scabies infestation is frequently seen in young infants. Sensitization after primary infestation takes 3–4 weeks before symptoms occur. With recurrent infestation, symptoms appear immediately. Performing a scabies preparation can confirm the diagnosis. Detection of evidence of scabies infestation is most likely by scraping linear burrows, vesicles, or papules that have not been excoriated. Interdigital spaces of the hands and feet, wrists, and axillae are often high-yield locations. Sometimes parents or other caregivers have papules or burrows that can be scraped as well.

The finding of mites, eggs, or feces on a scabies preparation using a microscope with a 10× objective confirms the diagnosis (Box 6.2). Mites have eight legs (Fig. 6.1); eggs are oval in shape and ten times smaller than mites; and feces, which are even smaller, appear as golden-brown clumps (Fig. 6.2). Air bubbles are round, which helps distinguish them from eggs or feces. Dermoscopy can also be useful in the diagnosis of scabies infestation (see below).

DERMOSCOPY

Dermoscopy (dermatoscopy or epiluminescence microscopy) is the examination of skin lesions with a handheld dermatoscope. Most dermatoscopes utilize polarized light to eliminate skin surface reflection. Specific patterns can be seen that help confirm

BOX 6.2 TECHNIQUE: SCABIES PREPARATION

1. Scrape the suspected lesion vigorously with the edge of a glass microscopic slide or a #15 blade. A drop of mineral oil can be placed on the lesion first, prior to scraping. The appearance of punctate bleeding signifies the proper depth.
2. Smear the scrapings onto a glass microscopic slide.
3. Apply 1 drop of mineral oil to the slide.
4. Place coverslip and gently press to remove any air bubbles.

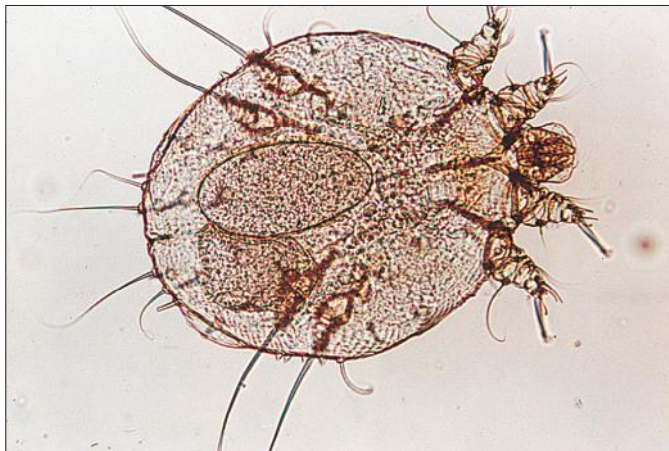


Figure 6.1 Scabies mite.

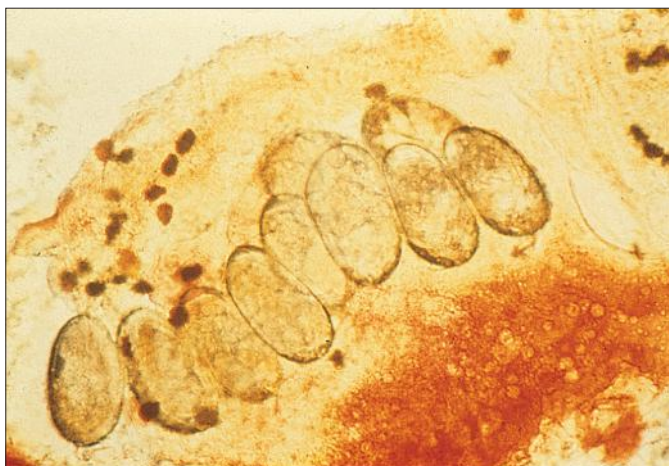


Figure 6.2 Scabies eggs and feces.

a suspected diagnosis. Dermoscopy can be useful in the identification of a broad set of conditions and lesions such as scabies mites or burrows; congenital and acquired melanocytic nevi including Spitz and blue nevi; and juvenile xanthogranuloma. The ‘triangle’ sign is the pigmented anterior portion of the scabies mite, which includes the head and first two pairs of legs,⁹ while ‘the jetliner with contrail’ sign represents the head of the mite along with the trailing burrow (Fig. 6.3).^{10,11} Typical Spitz nevi have four distinct dermoscopic patterns: starburst, globular, negative network, and homogeneous (Fig. 6.4).^{12,13} Histocytes laden with lipid give juvenile xanthogranulomas their characteristic yellow-orange color. Dermoscopy can show this orange-yellow background with an erythematous border, the



Figure 6.3 Scabies dermoscopy. Note 'triangle' and 'jetliner with contrail' signs. (Courtesy of Ashfaq Marghoob, MD. In: Haliasos EC, Kerner M, Jaimes-Lopez N, Rudnicka L, Zalaudek I, Malvey J, Hofmann-Wellenhof R, Braun RP, Marghoob AA. *Dermoscopy for the pediatric dermatologist. Part I: Dermoscopy of pediatric infectious and inflammatory skin lesions and hair disorders.* *Pediatr Dermatol* 2013; 30(2): 163–171.)

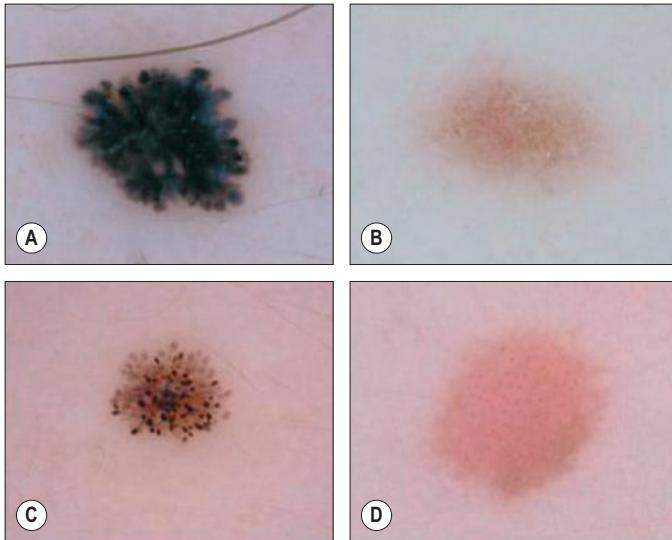


Figure 6.4 Spitz nevus dermoscopy. (A) Starburst pattern. (B) Negative network pattern. (C) Globular pattern. (D) Dotted vessel pattern. (Courtesy of Ashfaq Marghoob, MD. In: Haliasos EC, Kerner M, Jaimes N, Zalaudek I, Malvey J, Hofmann-Wellenhof R, Braun RP, Marghoob AA. *Dermoscopy for the pediatric dermatologist. Part III: Dermoscopy of melanocytic lesions.* *Pediatr Dermatol* 2013; 30(3):281–293.)

'setting sun' sign.¹⁴ Pale yellow 'clouds' can also be seen, which are thought to be lipid-laden histiocytes in the superficial dermis.¹⁴ Blue nevi have homogeneous, structureless pigment patterns of different colors (white or blue most commonly) or a combination of colors (Fig. 6.5).

MICROSCOPIC HAIR EXAMINATION

A number of hair shaft abnormalities can be detected by microscopic hair examination using a standard light microscope with and without a polarizing lens. Sharp iris scissors can be used to obtain hairs without the need to pluck them. A mounting medium such as Permout™, or immersion oil, and a cover slip



Figure 6.5 Blue nevus dermoscopy. Homogenous structureless pattern. (Courtesy of Ashfaq Marghoob, MD.)

may be used to mount the hairs on a glass slide. Only rarely is the hair bulb needed for diagnosis, such as with suspected loose anagen syndrome, in which case the hairs need to be gently pulled. Usually, an examination of scalp hair demonstrates the findings necessary for diagnosis; however, Netherton syndrome can be an exception, in which only eyebrow or eyelash hairs may have the characteristic findings. See [Chapter 31](#) for a discussion of hair disorders.

WOOD'S LIGHT EXAMINATION

A Wood's lamp is a handheld device fitted with a mercury lamp and a filter made of nickel oxide and silica. The light emitted from the device has wavelengths from 320 to 400 nm, which is the range in which melanin absorbs ultraviolet radiation. The lamp should be used in a dark room, so that ambient light does not interfere with the examination. Loss of melanin (depigmentation) appears as a 'bright white' area compared with surrounding normal skin. A Wood's lamp can be useful in the identification of vitiligo, tuberous sclerosis (ash leaf macules), and incontinentia pigmenti. Also, infected hairs fluoresce bright yellow-green in tinea capitis caused by *Microsporum canis*. The urine of neonates with congenital erythropoietic porphyria fluoresces coral red.¹⁵

SKIN BIOPSY

A skin biopsy can be very useful in determining a diagnosis. The tissue can be examined microscopically and it can also be cultured (bacterial, viral, fungal, mycobacterial). When the lesion is <6 mm in diameter, the entire skin lesion can be removed using a punch technique for both diagnostic and therapeutic purposes. The depth of the pathologic process determines how deep the skin specimen needs to be. Usually, a punch biopsy can be performed, since epidermis and dermis will be obtained, as well as the top layer of fat in some body locations ([Box 6.3](#)).

If a process or lesion involving the subcutaneous fat, such as panniculitis, is suspected, a 'double punch' method may be employed. One specimen is obtained and through the same defect, a second, deeper specimen is also obtained. This is often done with a larger sized punch trephine followed by a smaller one through the same defect, so that the hub does not become

BOX 6.3 TECHNIQUE: SKIN PUNCH BIOPSY

1. Choose the site. Consider the location, mobility of the child, and ability to hide the resulting scar. Do not biopsy skin overlying the fontanelles in a young infant without neurosurgical guidance because of the risk of disruption of the meninges.
2. Immobilize the child (see 'Immobilization', below).
3. Inject local anesthetic (see 'Injectable Anesthetics', below).
4. Rotate the punch trephine firmly into the skin. Pay attention to depth, so that the proper depth is ensured. In young infants, the dermis and subcutaneous fat are not as thick as in adults.
5. Pick up the sample gently with forceps and cut the bottom attachment with sharp iris scissors.
6. Place the specimen in formalin fixative for histology. For tissue cultures (bacterial, viral, fungal, mycobacterial), the specimen is obtained in the same manner and placed in a sterile cup with nonbacteriostatic saline-soaked gauze. This should be done *prior* to obtaining the specimen for histology.
7. For direct immunofluorescence (DIF), choose a perilesional site. The specimen is obtained in the same manner and placed in a sterile cup with saline-soaked gauze or Michel's transport medium or Zeus' fixative.
8. When cultures or DIF specimens are needed in addition to histology, some providers prefer to obtain one larger specimen (such as a 6 mm punch) that is then cut in half with a scalpel blade for each test.
9. Place sutures for hemostasis; a 5-0 non-absorbable suture such as nylon or polypropylene is usually adequate. Gelfoam® is an alternative in wounds that do not require suture.
10. Apply petroleum jelly or antibiotic ointment and a bandage.

stuck on the epidermal rim of the initial defect. For example, a 6 mm punch trephine can be used followed by a 4 mm punch trephine to obtain the second specimen. The specimens may be placed in separate formalin bottles.

If the pathologic process appears to have multiple morphologies, it may be necessary to obtain specimens from each type of lesion seen. When a specimen is needed for tissue culture, the tissue and instruments should not come in contact with formalin because the formalin will kill any organism, rendering the culture useless. Therefore, if specimens are needed for culture as well as histology, the culture specimen should be obtained first, so that no contamination occurs.

Once the specimen has been obtained, hemostasis is usually achieved with placement of sutures. In a neonate or young infant, a 5-0 non-absorbable suture such as nylon or polypropylene can be used. Some providers prefer to place Gelfoam® (Pharmacia and Upjohn Company, Kalamazoo, Michigan) in lieu of sutures depending on the size, location and type of lesion biopsied; however, the time to place one or two sutures is minimal and can result in a wound that heals more rapidly and a final smaller scar.

Shave procedures, also known as 'scoop biopsies' or 'saucerization biopsies' can be used instead of a punch trephine for biopsy or excision of superficial lesions that involve only the epidermis and superficial dermis. Either a DermaBlade® (Personna, Verona, Virginia) or #15 scalpel blade can be used to obtain the specimen.

ELECTRON MICROSCOPY

Electron microscopy requires extremely thin (one micrometer, 1 μ m) tissue sections and a special microscope to allow

visualization of cellular ultrastructure. It is most useful in neonates to localize the cleavage plane in epidermolysis bullosa (EB). When the diagnosis of EB is suspected, twisting a new, clean pencil eraser on normal-appearing skin just prior to skin biopsy is helpful to form a microscopic cleavage plane. Specimens should be obtained using the punch biopsy method outlined in 'Skin biopsy', above. Instead of placing the specimen in formalin, it should be placed in glutaraldehyde fixative. With the advent of genetic testing for EB with a blood specimen, electron microscopy is not necessary in many cases, especially if the mutation in the family is already known.

IMMUNOFLUORESCENCE

Immunofluorescence testing relies on the fluorescing of dyes to help localize immunoreactants in the skin or to determine their presence in the blood.

Direct immunofluorescence (DIF) may be useful in the diagnosis of immunobullous disorders, lupus erythematosus, and leukocytoclastic vasculitis. A skin biopsy should be taken from a perilesional location and placed in immunofluorescence transport medium (Michel's medium: ammonium sulfate, N-ethylmaleimide, magnesium sulfate in a citrate buffer). The specimen can be placed on saline-soaked gauze, as long as it is immediately transported to the laboratory and processed. The sample is incubated with antibodies to IgG, IgA, IgM, and C3 that have been labeled with a fluorescent marker. Fluorescence indicates the presence of the specific immunoglobulin or complement component.

Indirect immunofluorescence (IIF) is most useful in the diagnosis of immunobullous disorders such as pemphigus vulgaris and bullous pemphigoid. The patient's serum is incubated with an epithelial substrate to determine the circulating antibody titer. A modified IIF method on a skin specimen helps determine the ultrastructural level of antibodies in epidermolysis bullosa, which would be the most common use of the test in neonates. Laminin, type IV collagen, and bullous pemphigoid antigen are used, as well as other markers. Skin samples for this test are obtained in the same manner as for electron microscopy; a cleavage plane is induced with rotating pressure prior to obtaining the skin biopsy and the sample is placed in appropriate transport medium (i.e. Michel's or Zeus') prior to delivery to a laboratory skilled in antigenic mapping.

Therapeutic procedures

A number of therapeutic cutaneous procedures are commonly performed on neonates and young infants. These include skin biopsy (<6 mm in diameter), excision of cutaneous lesions, laser surgery, and injections. Proper immobilization and adequate anesthesia (topical, local and/or general) is required.

IMMOBILIZATION

Even with the use of topical and/or injectable local anesthetics, neonates and young infants will move during a procedure, and it is advisable to prevent as much movement as possible. There are a number of ways to do this. Restraining achieved by a staff member holding the infant is often adequate; however, supplemental techniques for immobilization are sometimes necessary. Some providers use wrapping techniques with cloth sheets, while others use a papoose board. Using a soft, cloth sheet is

BOX 6.4 TECHNIQUE: IMMOBILIZATION

1. Lay a folded cloth sheet (not paper) perpendicular across the table.
2. Place the child on the sheet. Be sure the shoulders are on the sheet, but the head is not on the sheet.
3. Wrap one side of the sheet over the closest shoulder and arm.
4. Pull the same half of the sheet underneath the back and buttocks.
5. Wrap the same half of the sheet over the other shoulder and arm.
6. Pull the sheet underneath the back and buttocks.
7. Any sheet left is wrapped over the abdomen.
8. The other half of the sheet is wrapped concentrically around the entire body until no loose ends remain.
9. Modifications can be made by:
 - a. Leaving an arm out.
 - b. Pushing up to see the leg.
 - c. Leaving out steps 6 and 7, so that the abdomen can be visualized.
 - d. Using a second sheet around the legs of a taller child.

(Modified from Lyon VB, Palmer CM, Wagner AM, Cunningham BB. Toddler wrap for abdominal biopsy or excision. *Pediatr Dermatol* 2008; 25(1):109–111.)

often viewed by parents as ‘gentle’ (Box 6.4, Fig. 6.6). In general, parents should not assist in the restraint of their child, but they often feel better if they can talk with their child; sometimes singing or playing music can be soothing. Distraction techniques used for older children such as reading a story or watching a video are not usually useful in this age group.

TOPICAL ANESTHETICS

Topical anesthetics can be useful in diminishing the pain of certain dermatologic procedures such as local anesthetic injection. They are usually safe with minimal side-effects. The most commonly used topical anesthetics are EMLA® (eutectic mixture of local anesthetics: 2.5% lidocaine and 2.5% prilocaine; Astra Zeneca, Wilmington, DE) and liposomal lidocaine (LMX® 4% or 5%, formerly ELA-Max®; Ferndale Healthcare Inc, Ferndale, MI).¹⁶

EMLA®

Application of EMLA® should be for 1 h with an occlusive dressing, yet adequate anesthesia can be achieved after 25 min on the face and other thin skin sites.¹⁷ Application on the mucosa may achieve anesthesia in 5–15 min due to faster

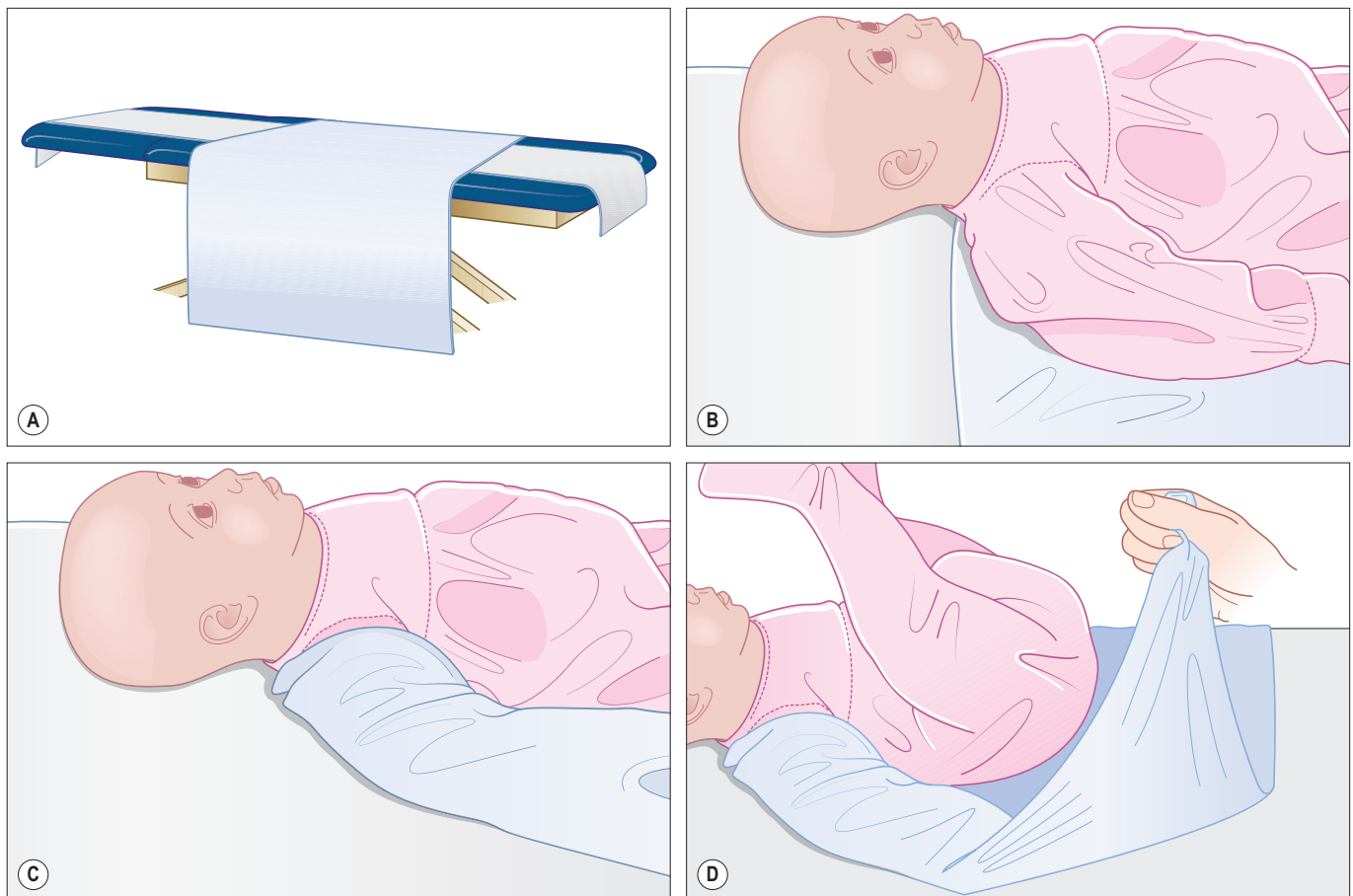


Figure 6.6 Immobilization. (A) Lay a folded cloth sheet (not paper) perpendicular across the table. (B) Place the child on the sheet. Be sure the shoulders are on the sheet, but the head is not. (C) Wrap one side of the sheet over the closest shoulder and arm. (D) Pull the same half of the sheet underneath the back and buttocks.

Continued

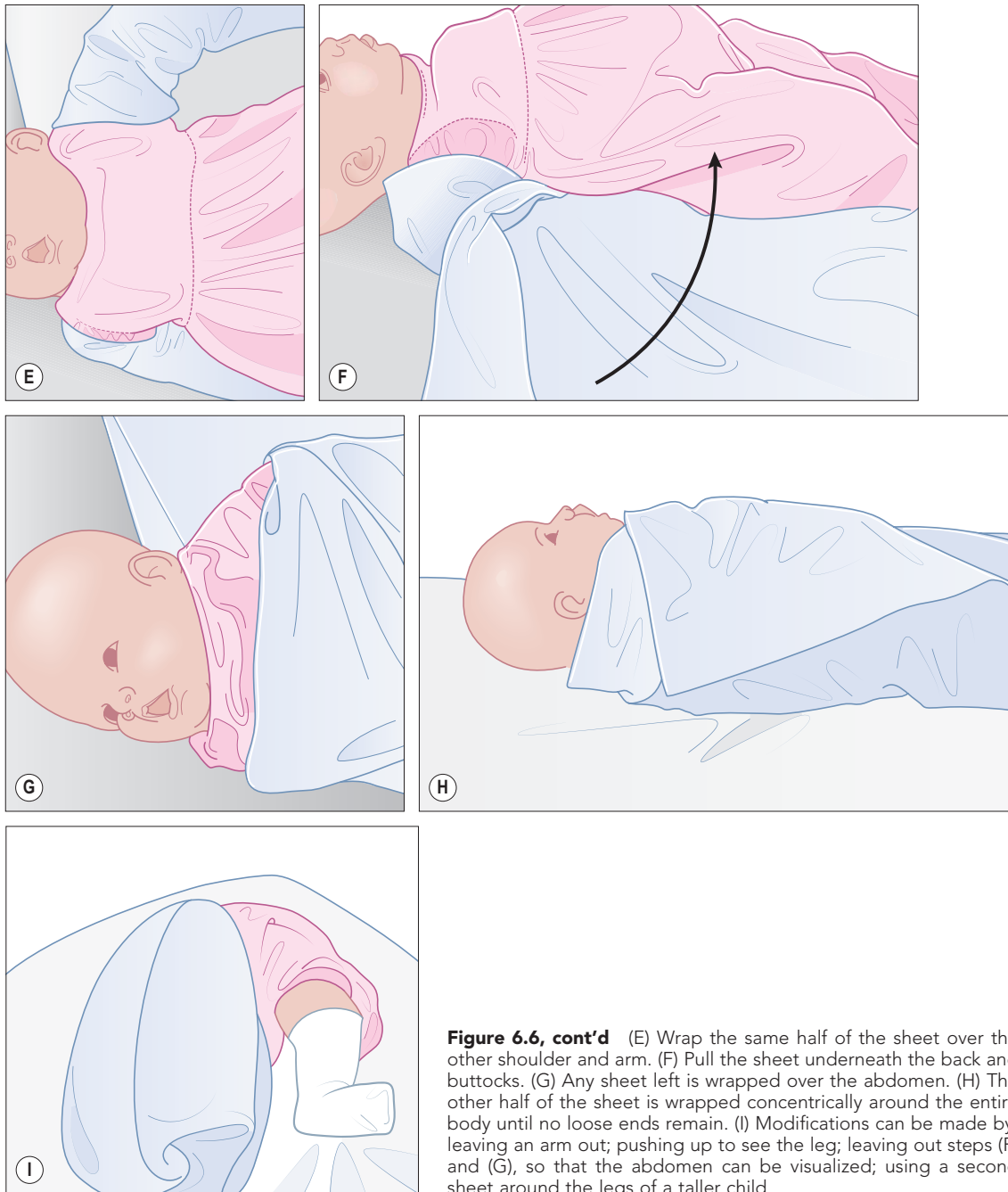


Figure 6.6, cont'd (E) Wrap the same half of the sheet over the other shoulder and arm. (F) Pull the sheet underneath the back and buttocks. (G) Any sheet left is wrapped over the abdomen. (H) The other half of the sheet is wrapped concentrically around the entire body until no loose ends remain. (I) Modifications can be made by: leaving an arm out; pushing up to see the leg; leaving out steps (F) and (G), so that the abdomen can be visualized; using a second sheet around the legs of a taller child.

absorption (Box 6.5, Table 6.1).¹⁸ EMLA® is available by prescription only.

Most infants tolerate EMLA® well. Side-effects such as vasoconstriction and blanching are common and more likely to occur with mucosal or broken skin application. They are self-limited and usually resolve within 3 h of removal.¹⁹ Erythema, edema, and dermatitis may also occur. Although petechiae and purpura can occur, these manifestations seem to be toxin-mediated and not allergic-mediated.^{20,21} They do not appear to be related to dose or to the duration of the application. Purpuric reactions have not been reported with topical lidocaine alone. While EMLA® has been used in the same individuals after this type of reaction without recurrence of purpura,²² repeat applications are generally avoided.

Methemoglobinemia can occur with exposure to local anesthetics containing prilocaine, such as EMLA®, especially in young infants because of their limited capacity to reduce methemoglobin.²³ This is why it is not recommended for infants who are of <37 weeks' gestation. Infants with hemoglobinopathies or glucose-6-phosphate dehydrogenase deficiency may also be at greater risk for the development of methemoglobinemia;^{24,25} so may infants <3 months of age who are taking acetaminophen, sulfonamides, phenobarbital, phenytoin, or antimalarial drugs.²⁴ Methemoglobinemia should be suspected in an infant with cyanosis who has no evidence of respiratory or cardiac disease and whose cyanosis does not improve with oxygen administration. Pulse oximetry is not accurate in this setting. Respiratory distress can occur with blood methemoglobin levels >20%, while

TABLE 6.1**EMLA® guidelines**

Age and weight of child	Maximum EMLA® dose (g)	Maximum area (cm ²)	Maximum application time (h)
<37 weeks' gestational age	Use not recommended	–	–
>37 weeks' gestational age	1	10	1
Up to 3 months OR <5 kg	1	10	1
>3 months and 5–10 kg	2	20	4

From: EMLA®: Prescribing information. Wilmington, DE 19850: AstraZeneca LP; 2005.

BOX 6.5 TECHNIQUE: APPLICATION OF EMLA® OR LMX® CREAM

1. Apply a thick layer to intact skin of interest.
2. Cover with occlusive dressing such as Tegaderm® or plastic wrap.
3. Apply for 30–60 min. Maximal effect usually seen at 1 h.
4. See Table 6.1 for EMLA® guidelines.

levels >50% can produce seizures and coma. Treatment with methylene blue is necessary for symptomatic patients.

Topical lidocaine (LMX®, formerly ELA-Max®)

Liposomal lidocaine (LMX®) is available in both 4% and 5% (as a rectal cream) over-the-counter preparations. An application time of 30 min without occlusion is recommended, although occlusion can be used to keep the cream in place. Because prilocaine is not in the product, the risk of methemoglobinemia is avoided. However, lidocaine toxicity can still occur and thus, small volumes of cream (<100 cm² for children <10 kg, or 1 g for infants from 37 weeks' gestational age to 3 months) and short application times are recommended for young infants. One study used 2 g of liposomal lidocaine applied for 20 min prior to circumcision, with good results.²⁶

INJECTABLE ANESTHETICS

The most commonly used injectable local anesthetics include lidocaine (Xylocaine®) and bupivacaine (Marcaine®, Sensorcaine®). They are available in a variety of strengths, as well as with and without epinephrine. For most dermatologic procedures, 1% lidocaine (10 mg/mL) with 1:100 000 epinephrine can be used. The onset of action is rapid – almost as soon as it is infiltrated, and vasoconstriction due to the epinephrine allows for ease of performing the procedure with decreased bleeding. Bupivacaine can be used for post-procedure pain with infiltration at the end of the procedure. Though it has a relatively slower onset of action (5–10 min), it lasts longer (3–4 h).

Lidocaine toxicity is rare as long as the dose is appropriate (Table 6.2). Knowledge of weight-based dosage limits is vital to ensure safe usage. Neonates are likely to be more susceptible to toxicity compared with older children because of increased bioavailability of the drug at a given serum concentration.²⁷ Detecting the signs of toxicity in neonates can be difficult. Confusion and agitation can progress to seizures, loss of consciousness, and respiratory depression.

For neonates and young infants, using an injectable anesthetic without prior topical anesthesia is acceptable and in some

Table 6.2**Lidocaine dosage for intralesional injection**

	Maximum dose	Example: maximum dose of 1% lidocaine (10 mg/mL) for 5 kg infant
Without epinephrine	4.5 mg/kg	2.25 mL
With epinephrine	7 mg/kg	3.5 mL

cases, preferable. The physician should forewarn the parents that infants undergoing a procedure often start to cry with restraining. Actual pain begins with injection of the needle and lasts only about 10–20 s during administration of the injectable anesthetic. After infiltration of local anesthetic and the provision of adequate anesthesia, infants will likely continue to cry, even though they are not experiencing any pain, simply because they dislike being restrained. It is important to inform the parents that even though the child may be crying while the biopsy is being obtained and sutures are being placed, they are not experiencing any pain.

GIVING AN INJECTION

Injections may be needed for a variety of reasons in young infants. Infiltration of local anesthetic prior to a procedure and intralesional corticosteroid injection of a hemangioma, are two examples. The best way to perform an injection is to ensure that the child is restrained in a way that is not harmful, but maximizes stability and therefore safety (see 'Immobilization', above). When giving an injection, there should be three points of contact (the syringe and two other points, which are usually the non-dominant hand and the fifth finger of the injecting hand). This method decreases any movement to prevent injecting the wrong area on the child or delivering a needle-stick to assistants or surgeon.

GENERAL ANESTHESIA

General anesthesia is required in order to perform some procedures on neonates and young infants. When making the decision whether a procedure should be done under general anesthesia, a number of factors are taken into consideration. The body location involved in the surgery is an important consideration, particularly when safety and/or the outcome could be compromised if the infant is awake. A biopsy near the eyelid margin would be one example. Another consideration is the length of the procedure. If the infant cannot be restrained for the time needed to perform the procedure, general anesthesia or sedation is likely indicated. Because dermatologic procedures usually take much less time than many other surgical

procedures, exposure to general anesthesia is minimal and therefore the risk of general anesthesia is very low.^{28,29}

WOUND CARE FOLLOWING A PROCEDURE

After a skin biopsy or excision has been performed, the wound must be cared for. Some providers recommend daily gentle cleansing of the site with plain water³⁰ or soap and water³¹ followed by application of petroleum jelly³² or an antibiotic ointment such as bacitracin.³³ The cleansing is followed by application of a fresh dressing each day. Typically, neomycin-containing ointments are not recommended due to the risk of developing allergic contact dermatitis. Other providers take a 'hands off' approach. In this method, a sterile dressing is applied over the wound immediately following the procedure. It remains in place and kept dry until the sutures are removed in the office. When using this method, the dressing is not altered in any way at home. Suture removal is usually recommended at 10–14 days for the body and scalp and 5–7 days for the face. For most small biopsy wounds, keeping the area moist with petroleum jelly and covered with a bandage, with a dressing change once a day is a reasonable approach.

LASER SURGERY

Laser (Light Amplification by Stimulated Emission of Radiation) light is used to treat a number of dermatologic disorders. The primary indication for its use in neonates and infants is for the treatment of capillary vascular malformations (CVM) (often termed port-wine stains) and for infantile hemangiomas. The flashlamp-pumped, pulsed dye laser (PDL) with a wavelength of 585–595 nm used with cooling spray is the most commonly used laser for these conditions. Oxyhemoglobin flowing through blood vessels has an absorption peak at 577 nm and is used as the chromophore. The settings usually range from 4 to 12 J/cm² fluence with a 1.5–10 ms pulse duration and 7–10 mm spot size. Cryogen settings are often changed depending on the Fitzpatrick skin type, which is a classification schema of skin color.³⁴ Treatment of CVM at a young age (<6 months) has been shown to yield better results,^{35,36} most likely due to thinner skin and more superficial vessels.³⁷ By starting laser surgery at a young age, multiple treatments can be performed just by using restraining methods in the laser suite (see 'Immobilization',

above) prior to the need for general anesthesia, and fewer total treatments may be needed.³⁸

Prior to laser treatment, the CVM can be outlined with a white eyeliner pencil³⁹ or a white gel pen.⁴⁰ This can be useful when the infant is in the laser suite where crying may produce erythema of the entire face or when under general anesthesia where fading of the stain due to possible vasodilation peripheral to the stain makes it more difficult to discern the lesion.^{41,42}

When laser treatment of the eyelids within the bony orbit is necessary, an eye shield needs to be placed to protect the globe. To place an eye shield in an awake infant, the globe must be anesthetized with a drop of an ophthalmic anesthetic such as proparacaine and an eye shield of appropriate size can be placed using ophthalmic lubricant, such as methylcellulose 1% ophthalmic drops or GenTeal® ophthalmic lubricant ointment (Novartis International AG, Basel, Switzerland). To place an eye shield in an infant under general anesthesia, only the lubricant is needed because there is no active resistance to placement of the eye shield.

Pulsed dye laser is useful in the treatment of residual telangiectasias and erythema following involution of hemangiomas.⁴³ Involution usually starts between 9 and 12 months of age and can continue for as long as 10 years. Pulsed dye laser treatment can also be helpful in individuals of any age with an ulcerated hemangioma.⁴⁴ Though most hemangiomas reach 80% of their ultimate size by 3 months of age during the proliferative phase,⁴⁵ the use of pulsed dye laser during this phase remains controversial. Some authors report good efficacy with minimal side-effects,⁴⁶ while others discuss complications such as ulceration and scarring when used to treat hemangiomas during the proliferative phase.⁴⁷

When counseling parents and guardians about possible laser treatment, it is helpful for them to see pictures of infants and children who have had laser treatment with 'before' and 'after' photographs, as well as pictures immediately after a laser treatment. Thus, they can have more realistic expectations of the procedure. For providers who perform pulsed dye laser treatment frequently, taking the time to make such a book of photographs is useful. Consent should be obtained from the parents to show pictures of their child in this way.

Access the full reference list at ExpertConsult.com 

KEY REFERENCES

6. Strick LB, Wald A. Diagnostics for herpes simplex virus: is PCR the new gold standard? *Mol Diagn Ther* 2006;10(1):17–28.
12. Argenziano G, Zalaudek I, Ferrara G, et al. Proposal of a new classification system for melanocytic naevi. *Br J Dermatol* 2007;157(2):217–27.
16. Friedman PM, Mafong EA, Friedman ES, et al. Topical anesthetics update: EMLA and beyond. *Dermatol Surg* 2001;27(12):1019–26.
28. Cunningham BB, Gigler V, Wang K, et al. General anesthesia for pediatric dermatologic procedures: risks and complications. *Arch Dermatol* 2005;141(5):573–6.
32. Draelos ZD, Rizer RL, Trookman NS. A comparison of postprocedural wound care treatments: do antibiotic-based ointments improve outcomes? *J Am Acad Dermatol* 2011;64(3 Suppl):S23–9.
34. Stier MF, Glick SA, Hirsch RJ. Laser treatment of pediatric vascular lesions: Port wine stains and hemangiomas. *J Am Acad Dermatol* 2008; 58(2):261–85.
36. Chapas AM, Eickhorst K, Geronemus RG. Efficacy of early treatment of facial port wine stains in newborns: a review of 49 cases. *Lasers Surg Med* 2007;39(7):563–8.
43. Maguiness SM, Frieden IJ. Current management of infantile hemangiomas. *Semin Cutan Med Surg* 2010;29(2):106–14.
46. Hunzeker CM, Geronemus RG. Treatment of superficial infantile hemangiomas of the eyelid using the 595-nm pulsed dye laser. *Dermatol Surg* 2010;36(5):590–7.
47. Witman PM, Wagner AM, Scherer K, et al. Complications following pulsed dye laser treatment of superficial hemangiomas. *Lasers Surg Med* 2006;38(2):116–23.

REFERENCES

- Friedlander SF, Pickering B, Cunningham BB, et al. Use of the cotton swab method in diagnosing tinea capitis. *Pediatrics* 1999;104(2):276–9.
- Hubbard TW, de Triquet JM. Brush-culture method for diagnosing tinea capitis. *Pediatrics* 1992;90(3):416–18.
- Bonifaz A, Isa-Isa R, Araiza J, et al. Cytobrush-culture method to diagnose tinea capitis. *Mycopathologia* 2007;163(6):309–13.
- Reisberger EM, Abels C, Landthaler M, et al. Histopathological diagnosis of onychomycosis by periodic acid-Schiff-stained nail clippings. *Br J Dermatol* 2003;148(4):749–54.
- Zirn JR, Tompkins SD, Huie C, et al. Rapid detection and distinction of cutaneous herpesvirus infections by direct immunofluorescence. *J Am Acad Dermatol* 1995;33(5):724–8.
- Strick LB, Wald A. Diagnostics for herpes simplex virus: is PCR the new gold standard? *Mol Diagn Ther* 2006;10(1):17–28.
- Hidalgo F, Melon S, de Ona M, et al. Diagnosis of herpetic keratoconjunctivitis by nested polymerase chain reaction in human tear film. *Eur J Clin Microbiol Infect Dis* 1998;17(2):120–3.
- Tremblay C, Coutlee F, Weiss J, et al. Evaluation of a non-isotopic polymerase chain reaction assay for detection in clinical specimens of herpes simplex virus type 2 DNA. Canadian Women's HIV Study Group. *Clin Diagn Virol* 1997;8(1):53–62.
- Hicks MI, Elston DM. Scabies. *Dermatol Ther* 2009;22(4):279–92.
- Argenziano G, Fabbrocini G, Delfino M. Epiluminescence microscopy: A new approach to in vivo detection of *Sarcoptes scabiei*. *Arch Dermatol* 1997;133(6):751–3.
- Haliasos EC, Kerner M, Jaimes-Lopez N, et al. Dermoscopy for the pediatric dermatologist part I: dermoscopy of pediatric infectious and inflammatory skin lesions and hair disorders. *Pediatr Dermatol* 2013;30(2):163–71.
- Argenziano G, Zalaudek I, Ferrara G, et al. Proposal of a new classification system for melanocytic naevi. *Br J Dermatol* 2007;157(2):217–27.
- Haliasos EC, Kerner M, Jaimes N, et al. Dermoscopy for the pediatric dermatologist. Part III: Dermoscopy of melanocytic lesions. *Pediatr Dermatol* 2013;30(3):281–93.
- Palmer A, Bowling J. Dermoscopic appearance of juvenile xanthogranuloma. *Dermatology* 2007;215(3):256–9.
- Hogeling M, Nakano T, Dvorak CC, et al. Severe neonatal congenital erythropoietic porphyria. *Pediatr Dermatol* 2011;28(4):416–20.
- Friedman PM, Mafong EA, Friedman ES, et al. Topical anesthetics update: EMLA and beyond. *Dermatol Surg* 2001;27(12):1019–26.
- Holmes HS. Choosing a local anesthetic. *Dermatol Clin* 1994;12(4):817–23.
- Rylander E, Sjöberg I, Lillieborg S, et al. Local anesthesia of the genital mucosa with a lidocaine/prilocaine cream (EMLA) for laser treatment of condylomata acuminata: a placebo-controlled study. *Obstet Gynecol* 1990;75(2):302–6.
- Villada G, Zetlaoui J, Revuz J. Local blanching after epicutaneous application of EMLA cream. A double-blind randomized study among 50 healthy volunteers. *Dermatologica* 1990;181(1):38–40.
- Calobrisi SD, Drolet BA, Esterly NB. Petechial eruption after the application of EMLA cream. *Pediatrics* 1998;101(3 Pt 1):471–3.
- Neri I, Savoia F, Guareschi E, et al. Purpura after application of EMLA cream in two children. *Pediatr Dermatol* 2005;22(6):566–8.
- Gourrier E, El Hanache A, Karoubi P, et al. [Cutaneous problems after application of EMLA in premature infants]. *Arch Fr Pediatr* 1996;3(3):289–90.
- Nilsson A, Engberg G, Henneberg S, et al. Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy. *Br J Anaesth* 1990;64(1):72–6.
- AstraZeneca. EMLA: Prescribing information. Wilmington, DE: AstraZeneca LP; 2005.
- Olson ML, McEvoy GK. Methemoglobinemia induced by local anesthetics. *Am J Hosp Pharm* 1981;38(1):89–93.
- Lehr VT, Cepeda E, Frattarelli DAC. Lidocaine 4% cream compared with lidocaine 2.5% and prilocaine 2.5% or dorsal penile nerve block for circumcision. *Am J Perinatol* 2005;22:231–7.
- Resar LM, Helfaer MA. Recurrent seizures in a neonate after lidocaine administration. *J Perinatol* 1998;18(3):193–5.
- Cunningham BB, Gigler V, Wang K, et al. General anesthesia for pediatric dermatologic procedures: risks and complications. *Arch Dermatol* 2005;141(5):573–6.
- Juern AM, Cassidy LD, Lyon VB. More evidence confirming the safety of general anesthesia in pediatric dermatologic surgery. *Pediatr Dermatol* 2010;27(4):355–60.
- Fernandez R, Griffiths R. Water for wound cleansing. *Cochrane Database Syst Rev* 2012;(2):CD003861.
- Noe JM, Keller M. Can stitches get wet? *Plast Reconstr Surg* 1988;81(1):82–4.
- Draeos ZD, Rizer RL, Trookman NS. A comparison of postprocedural wound care treatments: do antibiotic-based ointments improve outcomes? *J Am Acad Dermatol* 2011;64(3 Suppl):S23–9.
- Sheth VM, Weitzel S. Postoperative topical antimicrobial use. *Dermatitis* 2008;19(4):181–9.
- Stier MF, Glick SA, Hirsch RJ. Laser treatment of pediatric vascular lesions: Port wine stains and hemangiomas. *J Am Acad Dermatol* 2008;58(2):261–85.
- Geronemus RG, Quintana AT, Lou WW, et al. High-fluence modified pulsed dye laser photocoagulation with dynamic cooling of port-wine stains in infancy. *Arch Dermatol* 2000;136(7):942–3.
- Chapas AM, Eickhorst K, Geronemus RG. Efficacy of early treatment of facial port wine stains in newborns: a review of 49 cases. *Lasers Surg Med* 2007;39(7):563–8.
- Mariwalla K, Dover JS. The use of lasers in the pediatric population. *Skin Therapy Lett* 2005;10(8):7–9.
- Ashinoff R, Geronemus RG. Flashlamp-pumped pulsed dye laser for port-wine stains in infancy: earlier versus later treatment. *J Am Acad Dermatol* 1991;24(3):467–72.
- O'Regan GM, Benjamin LT. Delineating capillary malformations in the operating suite using white eyeliner pencil. *Pediatr Dermatol* 2011;28(6):746–7.
- Fenner JA, Scharf MJ, Wiss K. White gel pen easily marks a port-wine stain margin during pulsed dye laser therapy. *Dermatol Surg* 2011;37(12):1786.
- Tanaka K, Nakamura M, Domen M, et al. The influence of volatile anesthetics on portwine stain. *Clin Ther* 1993;15(3):567–9.
- Emhardt JD, Sadove AM, McNiece WL. Fading of a port-wine stain associated with sevoflurane anesthesia. *Anesth Analg* 1997;84(4):929–30.
- Maguiness SM, Frieden IJ. Current management of infantile hemangiomas. *Semin Cutan Med Surg* 2010;29(2):106–14.
- David LR, Malek MM, Argenta LC. Efficacy of pulse dye laser therapy for the treatment of ulcerated haemangiomas: a review of 78 patients. *Br J Plast Surg* 2003;56(4):317–27.
- Chang LC, Haggstrom AN, Drolet BA, et al. Growth characteristics of infantile hemangiomas: implications for management. *Pediatrics* 2008;122(2):360–7.
- Hunzeker CM, Geronemus RG. Treatment of superficial infantile hemangiomas of the eyelid using the 595-nm pulsed dye laser. *Dermatol Surg* 2010;36(5):590–7.
- Witman PM, Wagner AM, Scherer K, et al. Complications following pulsed dye laser treatment of superficial hemangiomas. *Lasers Surg Med* 2006;38(2):116–23.

Transient Benign Cutaneous Lesions in the Newborn

ANNE W. LUCKY

Introduction

Transient benign cutaneous lesions in the newborn are important to recognize. Not only can parents be reassured, but costly, unnecessary and erroneous evaluations and treatment of presumed serious diseases can be prevented. This chapter discusses the most common transient benign conditions seen in neonates. [Table 7.1](#) summarizes 15 studies of the incidences of transient benign cutaneous lesions.^{1–15} In some instances, racial and ethnic background may determine significant differences in the incidence of a disorder. Several excellent reviews of these conditions are also available.^{16–24}

Papules and pustules

MILIA

Milia are common papules that occur primarily on the face and scalp ([Fig. 7.1](#)). Clinically, they are tiny (up to 2 mm), white, smooth-surfaced papules, which are usually discrete, but their numbers may vary from a few to several dozen. They may be present at birth in 40–50% of newborns²⁵ or appear later in infancy. In a recent Spanish study of 1000 newborns, they occurred in 16.6%; 80% being on the face.²⁶ Although they usually occur on the face, they may be found anywhere. Milia are tiny inclusion cysts within the epidermis that contain concentric layers of trapped keratinized stratum corneum. Primary milia are associated with pilosebaceous units arising from the infundibula of vellus hairs. Secondary milia usually appear after trauma and originate from a variety of epithelial structures, such as hair follicles, sweat ducts, sebaceous ducts, or epidermis.²⁷ Neonatal milia are presumably primary. The diagnosis is a clinical one. If confirmation is needed, a small incision with the tip of a #11 blade can release the contents, which appear either as a smooth, white ball or keratinous debris.

The most important differential diagnosis of milia is from sebaceous hyperplasia (see below), which also presents with small white papules. However, sebaceous hyperplasia tends to be clustered around the nose and a bit more yellow, and occurs in large plaques. Milia may be associated with certain syndromes,²⁵ including epidermolysis bullosa, where lesions appear in sites of healing erosions, and in orofacial–digital syndrome type I, which features congenital mouth malformations, distinct facial features, and brachydactyly.²⁸ In these cases, milia are numerous and persistent.

Milia usually resolve spontaneously over several months without treatment. If persistent, lesions can be incised and expressed, but this is rarely necessary. Why they occur with increased frequency in the newborn period is unknown.

ORAL MUCOSAL CYSTS OF THE NEWBORN (PALATAL CYSTS OR EPSTEIN'S PEARLS, AND ALVEOLAR CYSTS OR BOHN'S NODULES) (SEE ALSO [CHAPTER 30](#))

Epstein's pearls and Bohn's nodules are actually both similar to milia,²⁵ being microkeratocysts^{29–31} located in the mouth. They are 1–2 mm, smooth, yellow to gray-white papules found singly or in clusters, most commonly on the median palatal raphe (68–81%). They also occur on the alveolar ridges (22%), more on the maxillary than the mandibular ridge, but rarely on both. They occur in 64–89% of normal neonates and are more common in Caucasian infants. A recent study from Taiwan of 420 neonates up to 3 days old examined by one dentist, revealed a 94% incidence of oral cysts.³²

Although there is no consistent use of nomenclature in the literature, usually when on the palate, these lesions have been called Epstein's pearls, and when on the vestibular or lingual surfaces of the alveolar ridges, Bohn's nodules ([Fig. 7.2](#)), and on the crest of the alveolar ridges, dental lamina cysts. The latter are thought to be derived from the ectoderm of the tooth bud.³³ Although Bohn and others had presumed that these were mucous gland cysts, more recent studies have shown them to be keratin cysts derived from the dental lamina. Both of these epidermal cysts occur in keratinized mucous membranes and form in embryonic lines of fusion. Epstein's pearls originate from epithelial remnants after fusion of palatal shelves. In a recent study of 1021 Swedish neonates,³¹ most of the palatal cysts had discharged spontaneously and resolved by age 5 months. Interestingly, 17 children developed new palatal cysts postnatally. However, most of the alveolar cysts regressed. A study of 60 premature compared with 60 term infants showed a lower prevalence in the prematures (9% vs 30%).³⁴ The diagnosis is clinical. Other congenital papules in the mouth include gingival (alveolar) cysts of the newborn, congenital epulis (granular cell tumor), lymphangiomas, mucocoeles, and ranulas (see also [Chapter 30](#)).²⁹

PERINEAL MEDIAN RAPHE CYSTS AND FORESKIN CYSTS

Other common locations for epidermal inclusion cysts are in the foreskin and along the ventral surface of the penis and scrotum ([Fig. 7.3](#); see [Fig. 9.8](#)).³⁵ These lesions tend to be larger than the milia that appear on the head and neck, and may represent a developmental abnormality of fusion with entrapment of epidermal or urethral cells. Histologically, they usually have a stratified squamous epithelial lining, but may have pseudostratified columnar epithelium or ciliated or mucus-secreting



Figure 7.3 A mucoid cyst on the median raphe of the penis in a neonate. (Courtesy of Dr A. Hernandez-Martin.)

TABLE 7.1	Incidence of common transient benign lesions in the neonate
	(%)
Epstein's pearls	56–89
Sebaceous hyperplasia	21–48
Erythema toxicum	7–41
Miliaria	1–15
Mongolian spots	
African-American	32.1–96
Asian	60–86
Latino	~65
Caucasian	3–13
Iranian	71
Salmon patch	
African-American	59
Asian	22
Latino	68
Caucasian	70
Iranian	26



Figure 7.1 Milia. Firm, white, smooth dome-shaped small papules on the chin of a newborn. (Courtesy of Dr A. Torrelo.)



Figure 7.2 Bohns' nodules. Microkeratocysts on the alveolar ridge of a newborn. (Courtesy of Dr A. Hernandez-Martin.)



Figure 7.4 Tiny superficial vesicles seen on the back and neck of this newborn are characteristic of miliaria crystallina.

cells as well, depending on which part of the urethra they are derived from. They often will enlarge throughout infancy and/or seem to appear after the newborn period, often in young men.³⁶ Some may be pigmented due to the presence of melanocytes and melanophages in the cyst lining.³⁷ They are benign and asymptomatic, although they may require surgical removal because of their large size or if they become infected.

MILIARIA

Miliaria is a general term for describing obstructions of the eccrine ducts.³⁸ It occurs in 1–15% of normal neonates (Table 7.1). Miliaria occurs in infants in warm climates, or those who are being kept warm or are febrile. It is thus more common in non-air-conditioned nurseries and in hot, rather than in temperate climates.^{4,6} The clinical manifestations of miliaria vary, depending on the level of the obstruction.

In the immediate newborn period, the most common form of miliaria is the most superficial, miliaria crystallina (sudamina). In miliaria crystallina, ductal obstruction is subcorneal or intracorneal. Obstruction at this level leads to very superficial trapping of sweat under the stratum corneum, producing typical small, crystal-clear vesicles that resemble water droplets on the skin (Fig. 7.4). These vesicles are extremely fragile and may be wiped away on cleansing of the skin. Miliaria crystallina usually appears in the first few days of life, but there are reports of congenital lesions.^{39–42} Occasionally, there will be many neutrophils within the lesions, giving them a more pustular than vesicular appearance. The causes of ductal blockage or leakage are not known. Some authors, however, favor the hypothesis that the ductal occlusion is caused by extracellular polysaccharide substance (EPS) from *Staphylococcus epidermidis*.⁴³ Miliaria crystallina is precipitated by environmental overheating or fever, with consequent superficial retention of sweat in the obstructed ducts and surrounding epidermis. The diagnosis is clinical, although a smear of the clear fluid contents of the vesicles shows an absence of cellular material or, at most, a few

neutrophils. Reducing the ambient temperature or treating the fever will prevent and/or treat miliaria. Miliaria crystallina is benign, but could be mistaken for more serious vesicular or pustular disorders such as herpes simplex.

Miliaria rubra is also common in overheated or febrile infants. Other terms for this disorder include 'heat rash' and 'prickly heat.' Miliaria rubra presents as erythematous, 1–3 mm papules or papulopustules on the head, neck, face, scalp, and trunk (Figs 7.5, 7.6). It can occur anywhere, but has a predilection for the forehead, upper trunk, and flexural or covered surfaces. The lesions are not follicular. When there is inflammation with multiple neutrophils in the lesions, as may be found under occlusion beneath monitor leads or bandages, miliaria rubra may look pustular and mimic worrisome conditions such as neonatal infections. Some authors subclassify this pustular form as miliaria pustulosa. Histologically, there is dermal inflammation around occluded eccrine ducts. The sweat duct obstruction is lower than in miliaria crystallina, but still intraepidermal. The diagnosis is made clinically, but if there is any doubt, a biopsy will confirm eccrine duct occlusion. The erythematous papules of miliaria rubra may mimic a variety of neonatal conditions, such as neonatal acne, as well as candidal, staphylococcal, or herpes simplex infections. Correcting the overheating is usually sufficient to manage miliaria.



Figure 7.6 Miliaria rubra in a 6-week-old infant.

Miliaria profunda, the third and deepest level of sweat duct obstruction, has occlusion at or below the dermoepidermal junction. It is rare in the newborn period. In older children and adults, this deep obstruction causes white papules representing dermal edema and can prevent adequate sweating, leading to hyperthermia.

SEBACEOUS HYPERPLASIA

Sebaceous hyperplasia is most prominent on the face, especially around the nose and upper lip, where the density of sebaceous glands is highest. It occurs in 21–48% of normal newborns (Table 7.1). Sebaceous hyperplasia appears as follicular, regularly spaced, smooth white-yellow papules grouped into plaques (Figs 7.7, 7.8). There is no surrounding erythema. Hormonal (androgen) stimulation in utero, which comes from either the mother or the infant, causes hypertrophy of sebaceous glands. Premature infants are less affected, but sebaceous hyperplasia occurs in nearly half of term newborns.^{6,7} Sebaceous hyperplasia gradually involutes in the first few weeks of life. The papules differ from milia, which are epidermal inclusion cysts, and are usually discrete, solitary, and whiter in color.

ERYTHEMA TOXICUM NEONATORUM (TOXIC ERYTHEMA OF THE NEWBORN, 'FLEA BITE' DERMATITIS)

Erythema toxicum is unquestionably the best-known benign eruption in the newborn period, occurring in approximately half of term newborns.^{40,43–45} Estimates of the incidence in large series range from 7% to 41% (Table 7.1), but frequencies as high as 72% have been reported.⁴⁴ In a recent Spanish study of 1000 newborns, 16.7% were found to be affected in the first 72 h of life.⁴⁶ The discrepancies in estimates of incidence may be due to the length of time these infants were observed. The presence of erythema toxicum has been well correlated with birthweight

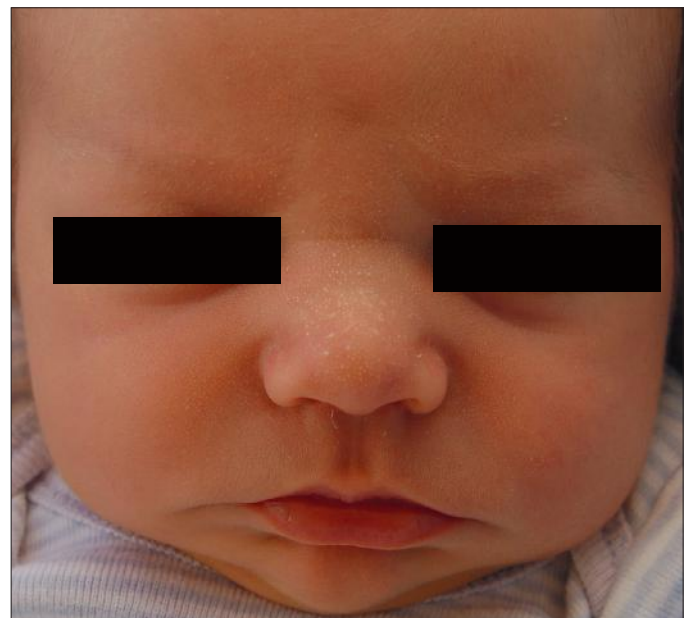


Figure 7.7 Sebaceous hyperplasia in a newborn.



Figure 7.5 Inflammatory papules and/or pustules of miliaria rubra are nonfollicular in distribution and are seen here on the scalp of an overheated newborn infant.



Figure 7.8 Sebaceous hyperplasia is typically located on and surrounding the nose, with sheets of tiny white-yellow follicular papules without inflammation.

and gestational age.⁴⁷ Other apparently associated environmental factors include first pregnancy, summer or autumn season, milk-powder feedings, vaginal delivery, and duration of labor.⁴⁸ It is virtually never seen in premature infants or those weighing <2500 g. There is no sexual or racial predilection.⁴⁹ Congenital lesions can occur,^{50–52} but the majority of cases have their onset between 24 and 48 h of life. Lesions wax and wane, usually lasting a week or less, but cases lasting beyond 7 days have been reported. Occasionally very atypical presentations are seen (i.e. onset as late as 10 days of age) and pustules contain predominantly neutrophils,^{49,53} but such cases require careful evaluation and skin biopsy to exclude other causes.

The classic eruption consists of barely elevated yellowish papules or pustules measuring 1–3 mm in diameter, with a surrounding irregular macular flare or wheal of erythema measuring 1–3 cm. The irregular shape of the flare has been likened to that of a flea bite (Figs 7.9A, 7.10). Although the characteristic lesions of erythema toxicum are usually discrete and scattered (Fig. 7.9B), extensive cases with either clusters of pustules, confluent papules, or pustules with surrounding erythema forming huge erythematous plaques can occur and be more difficult to diagnose (Fig. 7.9C). Lesions may appear first on the face and spread to the trunk and extremities, but may appear anywhere on the body except on the palms and soles.

Histologically, the lesions are eosinophilic pustules and characteristically intrafollicular, occurring subcorneally above the entry of the sebaceous duct.⁵⁴ This follicular location explains the absence of lesions on the palms and soles. Peripheral eosinophilia has also been associated in a minority (about 15%) of cases.

The etiology of erythema toxicum is unknown: a graft-versus-host reaction against maternal lymphocytes has been postulated as a possible mechanism,⁵⁵ but recent studies failed to show the presence of maternal cells in these lesions.⁵⁶ Another theory proposes an immune response to microbial colonization through the hair follicles as early as 1 day of age.⁵⁷ Immunohistochemical analysis of lesions from 1-day-old infants supports the accumulation and activation of immune cells in erythema toxicum lesions.⁵⁸

A variety of inflammatory mediators such as IL-1 α , IL-1 β , IL-8, eotaxin, aquaporins 1 and 3, psoriasin, nitric oxide synthetases 1, 2 and 3, and HMGB-1 have been associated with erythema toxicum immunohistochemically.^{45,59} Tryptase-expressing mast cells (but not the cathelicidin antimicrobial peptide LL-37) have been located in erythema toxicum biopsy specimens.⁶⁰

The diagnosis of erythema toxicum can usually be made by clinical appearance alone, but simple scraping of the pustule,



Figure 7.9 Erythema toxicum. (A) Erythematous macules and wheals may predominate. (B) In some cases, pustules are sparse. (C) Many patients have an admixture of wheals and pustules. (D) In other cases, extensive pustules predominate.



Figure 7.10 Erythema toxicum on the back of a neonate showing tiny papulopustules with surrounding flare. (Courtesy Dr A. Hernandez-Martin.)

smearing the contents onto a glass slide, and staining with Wright or Giemsa stain will reveal sheets of eosinophils with a few scattered neutrophils. Skin biopsy is rarely needed.

The differential diagnosis of erythema toxicum includes other pustular disorders of the newborn: infantile acropustulosis has a more acral rather than truncal distribution; herpes simplex has a more vesicular character, with subsequent crusting; staphylococcal impetigo has more well-developed pustules; congenital candidiasis has a positive KOH and can be more scaly. Transient neonatal pustular melanosis (TNPM) (see below) has primarily neutrophils in the infiltrate and is present at birth, and the pustules quickly disappear, leaving pigmented macules, but erythema toxicum and TNPM may appear together in some infants. Miliaria rubra can also present with erythematous papulopustules, but these favor the head and neck and are smaller lesions without the erythematous flare. No therapy is needed for erythema toxicum except for parental reassurance.

TRANSIENT NEONATAL PUSTULAR MELANOSIS

This disorder was first described in 1976,⁶¹ although it had undoubtedly occurred before that time. In fact, an abstract in

1961⁶² is likely to give the first description of TNPM, which was then called 'lentiginis neonatorum.' It occurs primarily in full-term African-descent infants in both sexes. In the 1976 report, 4.4% of African-American and 0.6% of Caucasian infants were affected.⁶¹ Lesions were always present at birth.

TNPM has three phases and hence three types of lesion. First, very superficial vesicopustules, ranging in size from 2 mm to as large as 10 mm, may be present in utero and are virtually always evident at birth (Fig. 7.11A). Because they are intracorneal and subcorneal, and thus very fragile, the pustules may be easily wiped away during the initial cleaning of the infant to remove vernix caseosa, so that the pustular phase may not be evident (Fig. 7.11B). The second phase is represented by a fine collarette of scale around the resolving pustule (Fig. 7.11C). The third phase consists of hyperpigmented brown macules at the site of previous pustulation (Fig. 7.11D). Although these macules have been called 'lentiginis' (because of their resemblance to lentils), they are not true lentiginis but appear to represent transient postinflammatory hyperpigmentation. They may last for up to several months before they fade. Some infants are born with these macules, the pustular phase having presumably occurred in utero. The most common location for TNPM has been under the chin, on the forehead, at the nape, and on



Figure 7.11 (A) Transient neonatal pustular melanosis first appears as small, superficial pustules without inflammation. (B) Collarettes of scale, typical of the second stage, are occasionally seen at birth without evident pustules (C), or may develop after pustules have ruptured. (D) The final stage is that of small hyperpigmented macules resembling lentils, which gradually fade over weeks to months.

TABLE
7.2

The differential diagnoses of transient benign pustular disorders in the neonate

	TNPM	ETOX	Miliaria	Infantile acropustulosis ^a	Eosinophilic pustulosis ^a
Onset	Birth	24–48 h	Birth or later	2–4 months	2–4 months
Course	6 months	Weeks	Days	Months to years	Months to years
Smear	Polys + Eos	Eos	Polys	Polys	Eos
Location	Trunk	All but palms and soles	Anywhere overheated, usually head, neck and trunk	Hands and feet	Scalp and face

TNPM, transient neonatal pustular melanosis; ETOX, erythema toxicum.

^aSee Chapter 10 for further discussion.

the lower back and shins, although the face, trunk, palms, and soles are also affected.

The etiology of TNPM is unknown. However, some authors^{63,64} have postulated that TNPM is a precocious form of erythema toxicum neonatorum, with clinical and histologic overlap. They have proposed the term sterile transient neonatal pustulosis to describe this overlap entity.⁶⁵ It is more likely, however, that these two conditions, which are both common, may coexist. In most infants there is little confusion based either on clinical appearance or time of onset.

Smears of the contents of the pustules stained with Giemsa or Wright stain show predominantly neutrophils, although a few eosinophils have also been reported. A biopsy is rarely needed for diagnosis. Histologically, these lesions consist of subcorneal pustules filled with neutrophils, fibrin, and rare eosinophils.⁶³ The differential diagnoses of transient benign pustular disorders in the neonate are summarized in Table 7.2. These benign conditions should be distinguished from neonatal staphylococcal infection, which would have a positive Giemsa stain on smear for polys and Gram-positive cocci and a positive bacterial culture, and for neonatal candidiasis, which would have a positive KOH examination for branching pseudohyphae and spores, as well as positive fungal cultures.

NEONATAL ACNE (CEPHALIC PUSTULOSIS)

So-called neonatal acne (see Chapters 10 and 25) is one of the most common transient conditions in neonates and young infants. This condition is *not* truly a form of acne vulgaris, which has distinguishing features such as comedones and larger inflammatory papules and pustules (Figs 7.12, 7.13) (see Chapter 25). Instead it is characterized by smaller inflammatory papules and pustules more reminiscent of miliaria. The nosology and etiology of this common disorder are debated: is it a form of acne or another pustular disorder of infancy? The term ‘neonatal cephalic pustulosis’ has been proposed to replace the term neonatal acne, and both continue to be used. Neonatal acne may occur at birth but more typically appears within the first few weeks of life. Classically, neonatal acne has been described as inflammatory, erythematous papules and pustules, located primarily on the cheeks, but scattered over the face and often extending onto the scalp. Coexistence with fine scaling in the scalp and eyebrows also raise a relationship to seborrheic or atopic dermatitis (Fig. 7.14). In addition, clinical differentiation between neonatal acne and miliaria rubra may be impossible in some cases. Biopsies would aid in diagnosis, but they are not justified, as both conditions are benign and transient.

Comedones are absent. It has been hypothesized that this condition may represent an inflammatory reaction



Figure 7.14 (A,B) Neonatal cephalic pustulosis, also called neonatal ‘acne’, is usually found on the cheeks and scalp in the first 2–4 weeks of life; small red papules and pustules without comedones are evident.

to *Pityrosporum* (*Malassezia*) species, both *M. furfur* and *M. sympodialis*. Treatment is usually not needed, however either an imidazole cream or low-potency topical corticosteroid, e.g. hydrocortisone 1%, may be useful in particularly severe cases.

Sucking blisters, erosions, pads, and calluses

Sucking blisters, erosions, and calluses on the hands and forearms are present at birth and can be solitary or bilateral.⁶⁶ Although the primary lesion from sucking is usually a tense,



Figure 7.12 (A,B) True infantile acne. This is a form of acne vulgaris with the features of adolescent acne, including open and closed comedones and inflammatory papules. (C) Infantile acne in a girl age 2 months.



Figure 7.13 Infantile acne on the cheek of an infant. (Courtesy of Dr L. Eichenfield.)

fluid-filled blister on normal-appearing skin (Fig. 7.15), when the blister has ruptured an erosion may result. If the sucking has been less vigorous and more chronic, the lesion may become a callus. These lesions appear to result from repetitive vigorous sucking in utero at one particular site. Often when the neonate is presented after birth with the affected extremity, he/she will immediately demonstrate sucking behavior on that area. Sucking blisters on the extremities may be mistaken for other serious disorders such as herpes simplex, but their solitary, asymmetric nature and characteristic location should help to establish the correct diagnosis.

In infants who are vigorous suckers postnatally, sucking pads or calluses can also occur on the lips (Fig. 7.16 and see Fig. 27.9). These occur postnatally and should be differentiated from the lesions on the extremities. Sucking calluses appear on the mucosa caudal to the closure line of infants' lips and are hyperkeratotic pads which eventually desquamate over 3–6 months.^{67,68} Histologically, there is epithelial hyperplasia and intracellular edema secondary to friction. No therapy is required.



Figure 7.15 A solitary, tense bulla arising on normal skin on the wrist of this infant is characteristic of a sucking blister. When presented with the extremity, the neonate preferentially sucked on this location.



Figure 7.16 Sucking callus on the lower lip of an infant. There are also two milia above the left side of the upper lip. (Courtesy of Dr A. Torrelo.)

Umbilical granuloma, patent urachus and omphalomesenteric duct remnant (umbilical polyp)

In some neonates, granulation tissue develops at the umbilical stump after the cord dries up and falls off, usually 6–8 days after birth. In most infants, the raw surface of the umbilicus heals within 12–15 days.^{69,70} Umbilical granulomata are grayish-pink papules on the umbilical stump (Figs 7.17, 7.18). They are extremely friable and bleed easily on touching. They have a 'velvety' feel to the surface.

The etiology of umbilical granulomas is failure of the surface of the proximal portion of the cord to heal and subsequent proliferation of endothelial cells without atypia.⁷¹ The term granuloma is misleading, because these lesions are composed of proliferating endothelial cells, like pyogenic granulomas, and are not true granulomas.

The diagnosis is usually made clinically and confirmed with resolution with topically applied silver nitrate. However, it is important to distinguish umbilical granulomas from other embryonic remnants. The normal umbilical cord consists of two umbilical arteries, one umbilical vein, a rudimentary allantois attached to the bladder (urachus), and a remnant of the vitelline (omphalomesenteric duct) attached to the ileum.⁶⁹ The proximal end of the vitelline duct creates Meckel's diverticulum. A patent urachus will intermittently discharge urine. A persistent vitelline duct will have a malodorous discharge. An umbilical polyp is a distal remnant of the vitelline duct that creates an erythematous papule similar in appearance to an umbilical granuloma, but the surface is sticky because of mucus secreted from the intestinal mucosa (see Fig. 9.33);⁷² rarely, both remnants are present in the umbilical lesion.⁷³ These developmental lesions all require surgical therapy. When talc-containing powders are used on the umbilical stump, talc granulomas can also form and look identical to umbilical granulomas.

The traditional treatment of umbilical granulomas is topical application of silver nitrate. Care must be taken to very lightly touch only the granulomas; otherwise chemical burns may occur on the surrounding normal skin.⁷⁴ If lesions fail to respond to one or two treatments, then serious consideration should be given to alternative diagnoses. Most umbilical granulomas are seen and treated by pediatricians and rarely come to the attention of the dermatologist.



Figure 7.18 A bright red, friable, glossy papule in the umbilicus is typical of an umbilical granuloma.



Figure 7.17 This friable, red papule arising from the umbilical stump is a typical umbilical granuloma.

Color changes in the newborn (Box 7.1)

PIGMENTARY ABNORMALITIES RESULTING FROM ABNORMALITIES OF MELANIN

Dermal melanosis (Mongolian spots)

Mongolian spots are collections of melanocytes located in the dermis. They are macules or patches that may be solitary and measure a few millimeters, or multiple and several centimeters in size. They are a distinctive slate blue, gray, or black (Figs 7.19, 7.20, 7.21) and are most commonly located over the buttocks and sacrum, but often occur elsewhere.^{2,75} Over the buttocks, Mongolian spots are seen in up to 96% of African-American, 86% of Asian, 65% of Latino and 13% of Caucasian neonates. In the sacral location, they usually resolve over several years.

Similarly appearing dermal melanosis in other locations such as the arms and shoulders (nevus of Ito), around the cheek and eye, including the sclera (nevus of Ota),⁷⁶ or elsewhere on the body (Fig. 7.22), may not resolve at all. The blue color of

dermal melanosis is a result of the Tyndall effect, in which red wavelengths of light are absorbed and blue wavelengths are reflected back from the brown melanin pigment located deep in the dermis. The pathogenesis is postulated to be a defect in migration of pigmented neural crest cells, which usually reside at the dermoepidermal junction. Histologically, spindle-shaped melanocytes are dispersed within dermal collagen. No treatment is recommended for dermal melanosis. Extensive Mongolian spots have been described in infants with GM1 gangliosidosis (see Chapter 24) and phakomatosis pigmentovascularis (see Chapter 23).

The pigmentation of nevus of Ota has been successfully treated with the Q-switched ruby laser.^{76,77} Small risks of melanoma and glaucoma exist for a nevus of Ota. It is most important to distinguish dermal melanosis from bruising, which would undergo a sequential color change from blue-black to green to yellow, so that there is no confusion about possible child abuse.

BOX 7.1 COLOR CHANGES IN THE NEONATE

PIGMENTARY

1. Melanin
 - a. Dermal melanosis (Mongolian spots)
 - b. Hyperpigmentation
 - c. Hypopigmentation
2. Non-melanin
 - a. Bilirubin
 - b. Meconium
 - c. Vernix

VASCULAR

1. Vasomotor instability
 - a. Cutis marmorata
 - b. Acrocyanosis
 - c. Harlequin color change
2. Rubor
3. Twin transfusion
4. Transient capillary vascular malformations

TRANSIENT EPIDERMAL HYPERPIGMENTATION

In more darkly pigmented neonates, transient, nearly black hyperpigmentation can be observed in the genital areas on the labia and scrotum (Fig. 7.23A,B), in a linear fashion on the lower abdomen (linea nigra), around the areolae, in the axillae, on the pinnae, and at the base of the fingernails (Fig. 7.23C).¹⁸ This is believed to be due to stimulation by melanocyte-stimulating hormone (MSH) in utero, but the mechanism is unclear.

Other nonhormonal patterns of brown hyperpigmentation have also been reported. Horizontal bands of hyperpigmentation corresponding to creases in the abdomen (Fig. 7.24A) or on the back seem to reflect flexion in utero.^{78–80} They are transient and tend to fade within 6 months. They are thought to be a result of mechanical trauma from hyperkeratosis within the folds. Transient reticulated or linear pigmentation on the back and knees has also been reported (Fig. 7.24B),⁸¹ presumably as a result of post-traumatic hyperpigmentation in utero.

The most important differential diagnosis of the neonate with hormonally induced hyperpigmentation is congenital adrenal hyperplasia (CAH). In this life-threatening condition there is massive stimulation by adrenocorticotrophic hormone (ACTH) resulting from an enzyme block in the synthesis of cortisol. The hyperpigmentation is believed to be due to cross-reactivity of ACTH with MSH receptors. Children with CAH also have ambiguous genitalia and will die if not promptly diagnosed and treated with replacement cortisol.

TRANSIENT HYPOPIGMENTATION

African-American and Asian infants often have much lighter overall pigmentation in the newborn period, which gradually darkens over the first year of life. Generalized hypopigmentation is also seen in genetic conditions such as phenylketonuria (PKU), Menkes' syndrome, Chediak-Higashi syndrome, and albinism. Non-transient but benign isolated hypopigmented macules and patches have been called nevus depigmentosus or, when in a segmental distribution, mosaic hypopigmentation. Such lesions can also be associated with genetic syndromes such as hypomelanosis of Ito and tuberous sclerosis (see Chapter 23).



Figure 7.20 Two infants with dermal melanosis 2 weeks and 5 months old. In this location, they will most likely fade over several years.



Figure 7.19 Dermal melanosis (Mongolian spots) on the back of an African-American infant, which will most likely fade over several years.



Figure 7.21 Dermal melanosis (Mongolian spots) on the back and buttocks. (Courtesy of Dr S. Friedlander.)



Figure 7.22 Dermal melanosis of the knee. The relatively sharp borders and location in this case suggest that it is less likely to be transient.

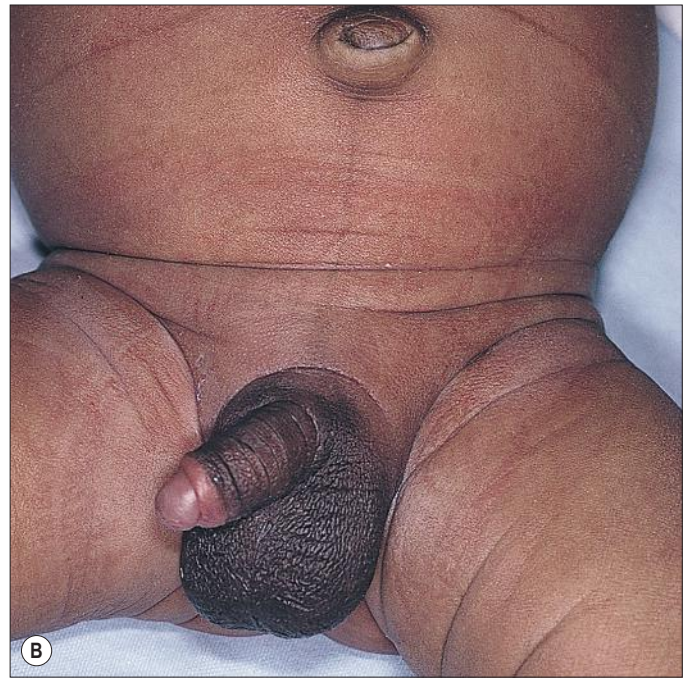


Figure 7.23 Intense hyperpigmentation. In neonates with dark skin, transient accentuation of nearly black pigmentation can be seen in several locations on the (A) vulva, (B) scrotum; (A,B) lower abdomen (linea nigra) and (C) base of the fingernails.

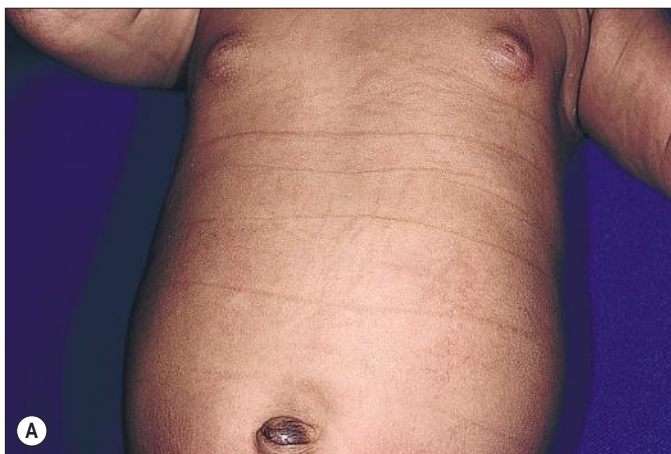


Figure 7.24 Horizontal linear hyperpigmentation in (A) the creases on the abdomen or (B) over the knees may be related to flexed positions and hyperkeratosis in utero.

TRANSIENT PIGMENTARY CHANGES NOT CAUSED BY MELANIN

Physiologic jaundice results from transient elevation of serum bilirubin, resulting in a generalized yellow discoloration of the skin in the first few days of life (Figs 7.25, 7.26). With jaundice, in contrast to carotenemia, which occurs later in infancy at age 1–2 years, there is yellow discoloration of the sclerae as well as the skin. Physiologic jaundice fades after the bilirubin returns to normal.

Meconium staining often will darken the vernix caseosa but can also leave patchy, yellow-brown pigmentation, especially on desquamating epidermis.

COLOR CHANGES RESULTING FROM VASCULAR ABNORMALITIES

Cutaneous vasomotor instability

The ability of neonates to adjust to extrauterine surroundings is at first immature, and they can exhibit distinct cutaneous blood flow abnormalities. When neonates are cold, their constricted capillaries and venules may produce a reticulated, mottled, blanchable, violaceous pattern termed cutis marmorata (Figs 7.27, 7.28). Exposure to cold temperatures may also induce more vasoconstriction in acral than central areas of the body, resulting in deep violaceous to blue coloration of the hands, feet and lips, termed acrocyanosis (Fig. 7.29). Both of these conditions occur more often in premature infants. These transient conditions rapidly improve upon rewarming of the infant, and the tendency to occur diminishes with age. Cutis marmorata should not be confused with cutis marmorata telangiectatica congenita, a vascular malformation that persists for several years and occurs in large, well-defined patches.

The so-called ‘harlequin’ color change is a rare physiologic phenomenon, whereby the amount of blood flow differs markedly on the right and left sides of the body, with a sharp cutoff at the midline.^{82,83} This is most often seen when a child is lying on one side, the dependent side exhibiting vasodilation and being strikingly redder than the upper half of the body (Fig. 7.30). The face and genitalia may be spared. Episodes last from seconds to minutes and are rapidly reversible with a change in



Figure 7.29 Acrocyanosis. Purplish discoloration of the feet on exposure to cold.

position or increased activity. It is more common in premature infants, but can affect up to 10% of full-term babies. Its onset is at 2–5 days of age, and the phenomenon lasts up to 3 weeks. There is no pathologic significance.

Rubor resulting from excessive hemoglobin

Because newborns have high levels of hemoglobin (16–18 g/dL) in the first weeks of life stimulated by in utero erythropoietin,⁸⁴ there is generalized rubor, which fades as the hemoglobin physiologically drops to normal levels. Twin transfusion may occur in twins as a result of shunting of blood from one to the other, resulting in a major color difference at birth, reflecting a marked discrepancy in hemoglobin levels between the two infants.

Capillary ectasias (nevus simplex, salmon patch)

Erythematous macules and patches occurring over the occiput, eyelids, glabella, and, to a lesser extent, the nose and upper lip are minor vascular stains consisting of ectatic capillaries in the upper dermis with normal overlying skin (Figs 7.31, 7.32, 7.33–7.37). They occur in 70% of Caucasian, 68% of Latino, 59% of



Figure 7.31 Nevus simplex on the midline of the face.



Figure 7.32 Nevus simplex (stork bite) on the occiput and nape of an infant.



Figure 7.25 Infant with jaundice undergoing phototherapy.



Figure 7.26 Neonate with severe jaundice. (Courtesy of Kerista Hansell MSN, RN.)



Figure 7.27 The legs of an infant with physiologic cutis marmorata. (Courtesy of Dr S. Friedlander.)



Figure 7.28 The legs of an infant with physiologic cutis marmorata.



Figure 7.30 Vasodilation of the dependent half of the body with a sharp midline cutoff is typical of a harlequin color change.

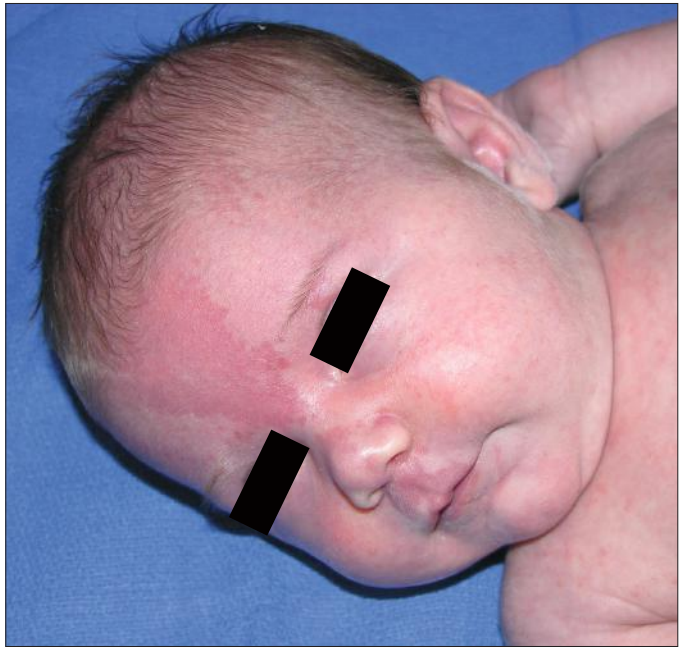


Figure 7.33 Nevus simplex on the mid-face.



Figure 7.34 Nevus simplex of the glabella, nose, lip and eyelid in a 3-month-old infant.



Figure 7.35 Nevus simplex on the nape.



Figure 7.36 A 3-month-old infant with a nevus simplex over the lumbosacral area. These are somewhat less likely to be transient; when associated with other lumbosacral birthmarks they may indicate underlying spinal dysraphism.



Figure 7.37 Salmon patch. An infant with salmon patch on the glabella, nevus, eyelids, nose and upper lip (A). The nape is the most common location for a salmon patch (B).

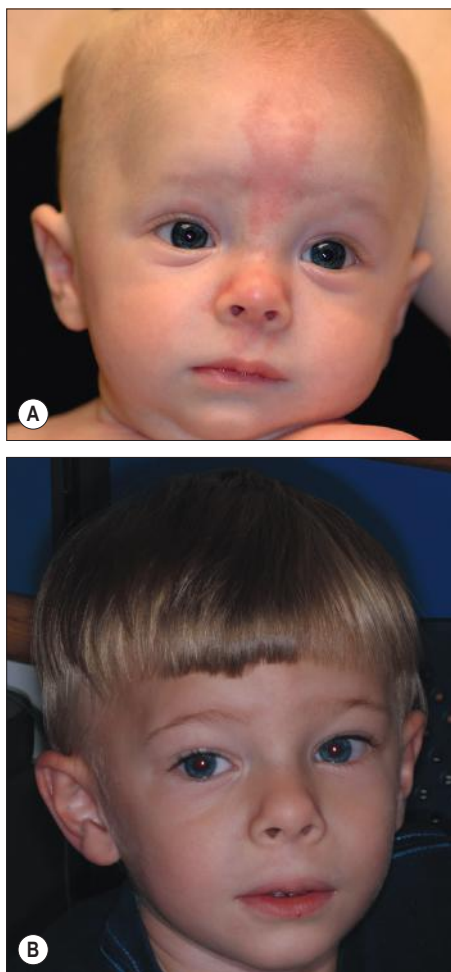


Figure 7.38 (A) Nevus simplex on the forehead, nose and upper lip of an infant. (B) The same child at age 3 years, with resolution of the vascular stain.

African-American, and 22% of Asian newborns,³ and have been given the common designations ‘angel’s kisses’ (eyelids) or ‘stork bites’ (nape) (Table 7.1). Most of the lesions resolve over several months to years (Figs 7.31, 7.38B), but 25–50% of nuchal lesions and a much smaller percentage of the glabellar lesions may persist into adult life. While the glabella, eyelids and nape are the most classic and characteristic locations for nevus simplex, more widespread involvement can be seen, including the vertex and occipital scalp, nose and perinasal skin, philtrum, lumbosacral skin and infrequently, the upper and mid-back. The more extensive form of nevus simplex is sometimes referred to as ‘nevus simplex complex’,⁸⁵ the primary differential diagnosis of these benign transient lesions with the other true capillary malformations (port-wine stains also known as ‘nevus flammeus’), which do not resolve. These are usually more lateral in location and often continue to darken and thicken with age. The transient stains, particularly the glabellar ones, are often inherited as an autosomal dominant trait.

Vernix caseosa

Vernix caseosa is notable on the surface of the skin at birth as a chalky-white mixture of shed epithelial cells, sebum, and sometimes hair (Fig. 7.39). The vernix presumably serves as a



Figure 7.39 The vernix caseosa is a white to gray, cheesy, greasy layer of sebum, keratin, and hair, which has protected the fetus in utero.

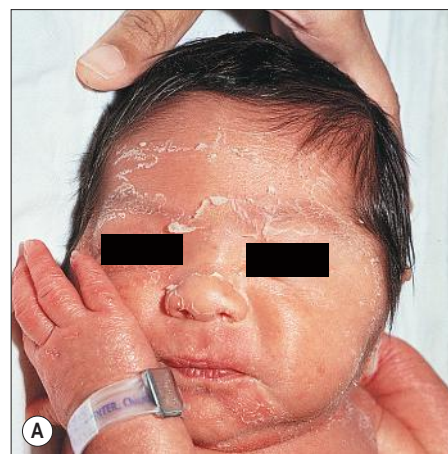


Figure 7.40 (A) Extensive desquamation can be a normal finding in the postmature infant. (B) Physiologic desquamation.

lubricant to protect the infant skin from amniotic fluid. It enhances skin hydration and provides a natural barrier. Recent studies support its role in natural defense from microbes because it contains antimicrobial peptides and lipids.⁸⁶ There is a marked difference in the biomarkers for structural proteins, cytokines and albumin during fetal maturation and its composition tends to favor wound healing and antimicrobial activity.^{87,88} It becomes thicker with advancing gestational age, although postmature infants usually have no vernix. In infants who have prepartum passage of meconium, the vernix may be stained yellow-brown, and this can be a clue to fetal distress.

Desquamation

Most full-term infants will have fine desquamation of the skin at 24–48 h of age. Premature infants do not show desquamation

until 2–3 weeks of life. The postmature infant, however, is often born with cracking and peeling of the skin that is much greater in intensity than in full-term or premature infants (Fig. 7.40). The differential diagnosis of physiologic desquamation includes various forms of ichthyosis, as well as hypohidrotic ectodermal dysplasia. These are discussed in detail in Chapters 19 and 29.

Access the full reference list at [ExpertConsult.com](https://www.expertconsult.com) 

Figures 3, 5, 8, 10, 12, 13, 17, 19, 21, 22, 25–28, 30, 33–37 are available online at [ExpertConsult.com](https://www.expertconsult.com)

KEY REFERENCES

- Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics* 1976;58:218–22.
- Alper JC, Holmes LB. The incidence and significance of birthmarks in a cohort of 4641 newborns. *Pediatr Dermatol* 1983;1:58–68.
- Kanada KN, Merin MR, Munden A, et al. A prospective study of cutaneous findings in newborns in the United States: correlation with race, ethnicity, and gestational status using updated classification and nomenclature. *J Pediatr* 2012;161(2):240–5.
- Berk DR, Bayliss SJ. Milia: a review and classification. *J Am Acad Dermatol* 2008;59(6):1050–63.
- Monteagudo B, Labandeira J, Cabanillas M, et al. Prospective study of erythema toxicum neonatorum: epidemiology and predisposing factors. *Pediatr Dermatol* 2012;29(2):166–8.
- Marchini G, Hultenby K, Nelson A, et al. Increased expression of HMGB-1 in the skin lesions of erythema toxicum. *Pediatr Dermatol* 2007;24(5):474–82.
- Ramamurthy RS, Reveri M, Esterly NB, et al. Transient neonatal pustular melanosis. *J Pediatr* 1976;88:831–5.
- Ladrigan MK, LeBoit PE, Frieden IJ. Neonatal eosinophilic pustulosis in a 2-month old. *Pediatr Dermatol* 2008;25(1):52–5.
- Kranbuhl KH, Lucky AW, Warner BW, et al. Combined omphalomesenteric and urachal remnants in an 18-month-old girl. *Pediatr Dermatol* 2007;24(1):65–8.
- Juern AM, Glick ZR, Drolet BA, et al. Nevus simplex: a reconsideration of nomenclature, sites of involvement, and disease associations. *J Am Acad Dermatol* 2010;63:805–14.

REFERENCES

- Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics* 1976;58:218–22.
- Cordova A. The Mongolian spot: A study of ethnic differences and a literature review. *Clin Pediatr Phil* 1981;20:714–19.
- Alper JC, Holmes LB. The incidence and significance of birthmarks in a cohort of 4641 newborns. *Pediatr Dermatol* 1983;1:58–68.
- Hidano A, Purwoko R, Jitsukawa K. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol* 1986;3:140–4.
- Osburn K, Schosser RH, Everett MA. Congenital pigmented and vascular lesions in newborn infants. *J Am Acad Dermatol* 1987;16:788–92.
- Nanda A, Kaur S, Bhakoo ON, et al. Survey of cutaneous lesions in Indian newborns. *Pediatr Dermatol* 1989;6:39–42.
- Rivers JK, Frederiksen PC, Dibdin C. A prevalence survey of dermatoses in the Australian neonate. *J Am Acad Dermatol* 1990;23:77–81.
- Tsai FJ, Tsai CH. Birthmarks and congenital skin lesions in Chinese newborns. *J Formos Med Assoc* 1993;92:838–41.
- Sachdeva M, Kaur S, Nagpal M, et al. Cutaneous lesions in new borns. *Indian J Dermatol Venereol Leprol* 2002;68(6):334–7.
- Moosavi Z, Hosseini T. One-year survey of cutaneous lesions in 1000 consecutive Iranian newborns. *Pediatr Dermatol* 2006;23(1):61–3.
- Shih IH, Lin JY, Chen CH, et al. A birthmark survey in 500 newborns: clinical observation in two northern Taiwan medical center nurseries. *Chang Gung Med J* 2007;30(3):220–5.
- Ferahbas A, Utas S, Akcakus M, et al. Prevalence of cutaneous findings in hospitalized neonates: a prospective observational study. *Pediatr Dermatol* 2009;26(2):139–42.
- Gokdemir G, Erdogan HK, Köşlü A, et al. Cutaneous lesions in Turkish neonates born in a teaching hospital. *Indian J Dermatol Venereol Leprol* 2009;75(6):638.
- Rodríguez-García C, Rodríguez C, Sánchez R, et al. Prevalence of cutaneous findings in Spanish neonates and relationships to obstetric and parental factors. *Pediatr Dermatol* 2012;29(2):232–3.
- Kanada KN, Merin MR, Munden A, et al. A prospective study of cutaneous findings in newborns in the United States: correlation with race, ethnicity, and gestational status using updated classification and nomenclature. *J Pediatr* 2012;161(2):240–5.
- Solomon LM, Esterly NB. Transient cutaneous lesions. In: *Neonatal dermatology*. Philadelphia: WB Saunders; 1973. p. 43–8.
- Schachner L, Press S. New clinical, diagnostic and therapeutic aspects of vesiculo bullous disorders in infancy and childhood. *Pediatr Ann* 1982;11:213–24.
- Rudolph AJ. *Dermatology and perinatal infection. Atlas of the newborn, vol. 4*. Hamilton, ON: BC Decker; 1997.
- Treadwell PA. Dermatoses in newborns. *Am Fam Phys* 1997;56:443–50.
- Van Praag MG, Van Rooij RG, Folkers E, et al. Diagnosis and treatment of pustular disorders in the neonate. *Pediatr Dermatol* 1997;14:131–43.
- Wagner A. Distinguishing vesicular and pustular disorders in the neonate. *Curr Opin Pediatr* 1997;9:396–405.
- O'Connor NR, McLaughlin MR, Ham P. Newborn skin: Part I. Common rashes. *Am Fam Physician* 2008;77(1):47–52.
- McLaughlin MR, O'Connor NR, Ham P. Newborn skin: Part II. Birthmarks. *Am Fam Physician* 2008;77(1):56–60.
- Su J. Common rashes in neonates. *Aust Fam Physician* 2012;41(5):280–6.
- Berk DR, Bayliss SJ. Milia: a review and classification. *J Am Acad Dermatol* 2008;59(6):1050–63.
- Monteagudo B, Labandeira J, Cabanillas M, et al. Prevalence of milia and palatal and gingival cysts in Spanish newborns. *Pediatr Dermatol* 2012;29(3):301–5.
- Lever WF, Schaumburg-Lever G. *Histology of the skin*. Philadelphia: JB Lippincott; 1990. p. 536.
- Larralde de Luna M, Raspa ML, Ibargoyen J. Oral-facial-digital type 1 syndrome of Papillon-Leage and Psamme. *Pediatr Dermatol* 1992;9:52–6.
- Eisen D, Lynch DP. Developmental disorders. The mouth: Diagnosis and treatment. St Louis: Mosby; 1998. p. 37–57.
- Jorgenson RJ, Shapiro SD, Salinas CF, et al. Intraoral findings and anomalies in neonates. *Pediatrics* 1982;69:577–82.
- Flinck A, Paludan A, Matsson L, et al. Oral findings in a group of newborn Swedish children. *Int J Paediatr Dent* 1994;4:67–73.
- Liu MH, Huang. Oral abnormalities in Taiwanese newborns. *J Dent Child* 2004;71:118–20.
- Cambiaghi S, Gelmetti C. Bohn's nodules. *Int J Dermatol* 2005;44(9):753–4.
- Donley CL, Nelson LP. Comparison of palatal and alveolar cysts of the newborn in premature and full term infants. *Pediatr Dent* 2000;22:321–4.
- LeVasseur JG, Perry VE. Perineal median raphe cyst. *Pediatr Dermatol* 1997;5:391–2.
- Nagor E, Sanchez-Motilla WH, Febrer JM, et al. Median raphe cysts of the penis: a report of five cases. *Pediatr Dermatol* 1998;15:191–3.
- Urahashi J, Hara H, Yamaguchi ZI, et al. Pigmented median raphe cysts of the penis. *Acta Dermatol Venereol* 2000;80:297–8.
- Feng E, Janniger C. Miliaria. *Cutis* 1995;55:213–16.
- Straka BF, Cooper PH, Greer KE. Congenital miliaria crystallina. *Cutis* 1991;47:103–6.
- Arpey CJ, Nagashima-Whalen LS, Chren MM, et al. Congenital miliaria crystallina: Case report and literature review. *Pediatr Dermatol* 1992;9:283–7.
- Haas N, Henz BM, Weigel H. Congenital miliaria crystallina. *J Am Acad Dermatol* 2002;47:S270–2.
- Gan VN, Hoang MP. Generalized vesicular eruption in a newborn. *Pediatr Dermatol* 2004;21:171–3.
- Mowad CM, McGinley KJ, Foglia A, et al. The role of extracellular polysaccharide substance produced by *Staphylococcus epidermidis* in miliaria. *J Am Acad Dermatol* 1995;33:729–33.
- Harris JR, Schick B. Erythema neonatorum. *Am J Dis Child* 1956;92:27–33.
- Morgan AJ, Steen CJ, Schwartz RA, et al. *Cutis* 2009;83(1):13–16.
- Monteagudo B, Labandeira J, Cabanillas M, et al. Prospective study of erythema toxicum neonatorum: epidemiology and predisposing factors. *Pediatr Dermatol* 2012;29(2):166–8.
- Carr JA, Hodgman JE, Freedman RI, et al. Relationship between toxic erythema and infant maturity. *Am J Dis Child* 1966;112:129–34.
- Liu C, Feng J, Qu R, et al. Epidemiologic study of the predisposing factors in erythema toxicum neonatorum. *Dermatology* 2005;210:269–72.
- Chang MW, Jiang SB, Orlow SJ. Atypical erythema toxicum neonatorum of delayed onset in a term infant. *Pediatr Dermatol* 1999;16:137–41.
- Levy HL, Cothran F. Erythema toxicum neonatorum present at birth. *Am J Dis Child* 1962;103:125–7.
- Marino LJ. Toxic erythema present at birth. *Arch Dermatol* 1965;92:402–3.
- Maffei FA, Michaels MG. An unusual presentation of erythema toxicum: scrotal pustules present at birth. *Arch Pediatr Adolesc Med* 1996;150:649–50.
- Berg FJ, Solomon LM. Erythema neonatorum toxicum. *Arch Dis Child* 1987;62:327–8.
- Luders D. Histologic observations in erythema toxicum neonatorum. *Pediatrics* 1960;26:219–24.
- Bassukus ID. Is erythema toxicum neonatorum a mild self-limited acute cutaneous graft-versus-host-reaction from maternal-to-fetal lymphocyte transfer? *Med Hypotheses* 1992;38:334–8.
- Droitcourt C, Khosrotehran K, Halaby E, et al. Maternal cells are not responsible for erythema toxicum neonatorum. *Pediatr Dermatol* 2008;25(3):411–13.
- Marchini G, Nelson A, Edner J, et al. Erythema toxicum neonatorum is an innate immune response to commensal microbes penetrated into the skin of the newborn infant.
- Marchini G, Ulfgren AK, Lore K, et al. Erythema toxicum neonatorum: an immunohistochemical analysis. *Pediatr Dermatol* 2001;18:177–87.
- Marchini G, Hulténby K, Nelson A, et al. Increased expression of HMGB-1 in the skin lesions of erythema toxicum. *Pediatr Dermatol* 2007;24(5):474–82.
- Nelson A, Ulfgren AK, Edner J, et al. Urticaria Neonatorum: accumulation of tryptase-expressing mast cells in the skin lesions of newborns with Erythema Toxicum. *Pediatr Allergy Immunol* 2007;18(8):652–8.
- Ramamurthy RS, Reveri M, Esterly NB, et al. Transient neonatal pustular melanosis. *J Pediatr* 1976;88:831–5.
- Perrin E, Sutherland J, Baltazar S. Inquiry onto the nature of lentiginos neonatorum: Demonstration of a statistical relationship with squamous metaplasia of the amnion. *Am J Dis Child* 1961;102:648–9.
- Barr RJ, Globberman LM, Werber FA. Transient neonatal pustular melanosis. *Int J Dermatol* 1979;18:636–8.
- Ladrigan MK, LeBoit PE, Frieden IJ. Neonatal eosinophilic pustulosis in a 2-month old. *Pediatr Dermatol* 2008;25(1):52–5.
- Ferrandiz C, Coroleu W, Ribera M, et al. Sterile transient neonatal pustulosis is a precocious form of erythema toxicum neonatorum. *Dermatology* 1992;185:18–22.
- Murphy WF, Langly AN. Common bullous lesions – presumably self-inflicted – occurring in utero in the newborn infant. *Pediatrics* 1963;32:1099–100.
- Heyl T, Raubenheimer EJ. Sucking pads (sucking calluses) of the lips in neonates: A manifestation

- of transient leukoedema. *Pediatr Dermatol* 1987;4:123–8.
68. Thariat J, Roth V, Marcy PY. Sucking pads in a full-term newborn. *J Pediatr* 2011;158(1):166.
 69. McCallum DI, Hall GF. Umbilical granuloma – with particular reference to talc granuloma. *Br J Dermatol* 1970;83:151–6.
 70. Andreassi L. Diseases of the umbilicus. In: Ruiz-Maldonado R, Parish LC, Beane JM, editors. *Textbook of pediatric dermatology*. Philadelphia: Grune & Stratton; 1989. p. 820–2.
 71. Johnson BL, Honig PG, Jaworsky C. *Pediatric dermatopathology*. Boston: Butterworth – Heinemann; 1994. p. 16–17.
 72. Pomeranz A. Anomalies, abnormalities and care of the umbilicus. *Pediatr Clin North Am* 2004; 819–27.
 73. Kranbuhl KH, Lucky AW, Warner BW, et al. Combined omphalomesenteric and urachal remnants in an 18-month-old girl. *Pediatr Dermatol* 2007;24(1):65–8.
 74. Daniels J, Craig F, Wajed R, et al. Umbilical granulomas: a randomized controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2003;88:F255–8.
 75. Levine N. Pigmentary abnormalities. In: Schachner LA, Hansen RC, editors. *Pediatric Dermatology*. 2nd ed. New York: Churchill Livingstone; 1995. p. 546–7.
 76. Sinha S, Cohen PJ, Schwartz RA. Nevus of Ota in children. *Cutis* 2008;82(1):25–9.
 77. Geronemus RG. Q-switched ruby laser therapy of nevus of Ota. *Arch Dermatol* 1992;128: 1618.
 78. Gibbs RC. Unusual striped hyperpigmentation of the torso. *Arch Dermatol* 1967;95: 385–6.
 79. Martín JM, Jordá E, Alonso V. Transient pigmentary lines of the newborn. *Pediatr Dermatol* 2009;26(6):768.
 80. Garg G, Bhalla M, Thami GP. Transient infantile patterned hyperpigmentation. *Pediatr Dermatol* 2012;29(3):372–3.
 81. Halper S, Rubenstein D, Prose N, et al. Pigmentary lines of the newborn. *J Am Acad Dermatol* 1993;28:893–4.
 82. Selimoglu MA, Dilmen U, Karakelleoglu C, et al. Harlequin color change. *Arch Pediatr Adolesc Med* 1995;149:1171–2.
 83. Januário G, Salgado M. The Harlequin phenomenon. *J Eur Acad Dermatol Venereol* 2011; 25(12):1381–4.
 84. Cordoro KM, Speetzen LS, Koerper MA, et al. Physiologic changes in vascular birthmarks during early infancy: Mechanisms and clinical implications. *J Am Acad Dermatol* 2009;60(4): 669–75.
 85. Juern AM, Glick ZR, Drolet BA, et al. Nevus simplex: a reconsideration of nomenclature, sites of involvement, and disease associations. *J Am Acad Dermatol* 2010;63:805–14.
 86. Bergsson TM, Kai-Larsen G, Lengqvist J, et al. Vernix caseosa as a multi-component defence system based on polypeptides, lipids and their interactions. *Cell Mol Life Sci* 2005;62:2390–9.
 87. Narendran V, Visscher MO, Abril I, et al. Biomarkers of epidermal innate immunity in premature and full-term infants. *Pediatr Res* 2010; 67(4):382–6.
 88. Visscher MO, Utturkar R, Pickens WL, et al. Neonatal skin maturation – vernix caseosa and free aminoacids. *Pediatr Dermatol* 2011;28(2): 122–32.

Iatrogenic and Traumatic Injuries

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Introduction

A variety of untoward events may befall the developing infant while in utero or postpartum. Some of these perinatal problems are inherent in the birth process. Others are related to technological advances that have become standard obstetric and nursery practice. Although these diagnostic and therapeutic procedures have reduced morbidity and mortality, some also pose a significant risk for iatrogenic complications. Sequelae of iatrogenic complications can also present later in infancy or early childhood. Moreover, iatrogenic and traumatic injuries can occur in older infants. This chapter emphasizes those occurring in neonates and young infants. More extensive discussions of non-accidental injury (more common in older infants) can be found in other textbooks.

Puncture wounds

AMNIOCENTESIS

Amniocentesis is currently the most widely used technique for the antenatal diagnosis of genetic disorders. Although routinely a second-trimester procedure, it may also be performed in the third trimester for management of isoimmunization or evaluation of fetal maturity, or late in the first trimester for fetal karyotyping and DNA analysis.¹ The risk of damage to the fetus is quite low, particularly in the middle trimester; nevertheless, needle puncture of the skin and sometimes of the underlying structures is a possible complication. Estimates of the incidence of cutaneous scarring ranged as high as 9% in the 1970s; however, with increased experience and the advent of real-time ultrasonography, this figure has dropped to less than 1%.² Despite the benignity of the procedure, the incidence of fetal injury rises dramatically with an increasing number of needle passages at amniocentesis.

Amniocentesis scars are depressed, dimple-like lesions that usually measure 1–5 mm in diameter, although scars as large as 12 mm in diameter and 8 mm in depth have been documented (Fig. 8.1). They may be solitary or multiple, and are often inconspicuous. Shallow linear lesions have also been described.² Although sometimes present at birth, they are often not noticed until the infant is several weeks to months old. The most frequent sites of injury are the extremities, followed by the head, neck, and chest. Mid-trimester amniocentesis has the lowest risk of puncture because the fetus occupies only about 50% of the amniotic cavity; in both the first and third trimesters, there is less room to maneuver, and sudden movements of the fetus may make injury unavoidable.

Amniocentesis scars must be differentiated from congenital sinus tracts, aplasia cutis, focal dermal dysplasia, amniotic band syndrome, accessory nipples, and dimples associated with

congenital rubella, diastematomyelia, Bloom syndrome, and cerebrohepatorenal syndrome.

CHORIONIC VILLUS SAMPLING

Chorionic villus sampling (CVS), which can be performed early in the first trimester, is the preferred procedure for patients at risk for certain single gene disorders. The technique yields mitotically active cells suitable for rapid DNA analysis and permits detection of placental mosaicism. Of concern, however, are reports of increased risk of limb and jaw malformations as well as an increased risk of infantile hemangiomas, particularly in fetuses undergoing CVS at <9 weeks' gestation.^{1,3} An analysis of 138 996 outcomes in a multicenter study disputes this notion⁴ but is not universally accepted, and thus the issue remains a controversial area still under study. A distinctive defect of absent distal third fingers with tapering of other digits, was more recently reported to be associated with exposure to CVS in a review by Golden and colleagues.⁵

FETAL MONITORING

Intrauterine electronic monitoring of the fetal heart rate via a spiral electrode attached to the presenting part has become standard obstetric practice. Complications are infrequent and consist mainly of minor lacerations, ulcerations, scalp abscesses, and herpetic infections.^{6,7} Herpetic infections are extremely rare; however, incidence figures for scalp abscesses in monitored infants due to other agents, range from 0.1% to 5.4%,^{8,9} with most in the 0.3–0.5% range.

Scalp abscesses are localized collections of suppurative material that present as erythematous, indurated masses with or without fluctuance in the area of electrode application. Usually solitary, they vary in size from one to several centimeters. Onset can be as early as the first day or as late as the third week, but they are most frequently noted on the third or fourth day of life. Enlarged posterior cervical lymph nodes often accompany the abscess. Usually the inflammation remains confined to the skin; however, in a review of neonatal scalp abscesses by Weiner and coworkers, reported complications can include osteomyelitis, cellulitis, seizures, meningitis, brain abscess, bacteremia, and death.¹⁰ Contributing factors in some series (but not others) appear to be high-risk pregnancy (prematurity), prolonged rupture of the membranes, and long duration of fetal heart rate monitoring. The presence of amnionitis^{6,8,11} does not seem to be correlated. Although an infectious cause has been disputed – because cultures obtained from some infants have been sterile – data from large series support the concept of an infectious etiology. Okada and colleagues⁸ reported on 42 infants with scalp abscess, 100% of whom had positive cultures: 85% were polymicrobial, 58% grew both aerobes and anaerobes, 33% grew



Figure 8.1 Deep dimple and scar on the buttock of an infant as a sequella of amniocentesis.

aerobes only, and 9% grew anaerobes only. The predominant aerobic organisms were *Staphylococcus epidermidis* and *Streptococcus* groups A and B; the predominant anaerobes were *Streptococcus* and *Peptococcus*. A confirmatory study by Brook and Frazier¹² demonstrated similar findings in 23 infants. Andrews and colleagues evaluated vaginal cultures from 5732 mothers and found the MRSA colonization rate to be 3.5%, with no cases of early-onset neonatal MRSA infection postpartum.¹³ It is critical to distinguish infants with intrapartum inoculation of herpes simplex virus (HSV) from neonates with a bacterial scalp abscess (see Chapter 13). Although HSV infection as a complication of scalp monitoring is distinctly uncommon, the outcome can be devastating, with permanent neurologic damage,¹⁴ or death from systemic disease.¹⁵ Both type 1,¹⁵ and type 2 infections⁷ have been documented; unfortunately, this complication may occur with asymptomatic shedding of the virus and in the absence of a history of overt clinical disease.

Scalp abscesses usually heal uneventfully but may leave minor degrees of scarring, hypopigmentation, and alopecia, causing confusion with aplasia cutis, nevus sebaceus, or focal dermal hypoplasia in later years.

NEEDLE MARKS AND SCARS

Needle marks consisting of hypopigmented pinhead-size lesions, when presenting in large numbers, may impart a speckled appearance to the skin. These marks are due to venipuncture, arterial punctures, and catheter insertion, and are most commonly seen on the scalp, hands, wrists, feet, ankles, arms, and legs. Fox and Rutter¹⁶ reported an improvement in the appearance of needle marks by 9 years of age, in their cohort of 90 patients. Heel-pricks from blood sampling may cause dimpling or, rarely, calcified nodules (see below), hypertrophic scars, or even gangrene (Fig. 8.2).

Birth-related trauma to the skin and scalp

Injury to the soft tissues may occur in the setting of a prolonged labor because of cephalopelvic disproportion (Fig. 8.3), or with forceps delivery. Erythema, abrasions, and forceps marks are most common over the face, but rarely cause significant injury, and usually resolve spontaneously (Fig. 8.4).



Figure 8.2 (A) Hemorrhage and skin necrosis of the heel from repeated punctures. (B) Multiple stellate scars secondary to heel-sticks in a premature infant.



Figure 8.3 Erythema and abrasions from delivery-related trauma.

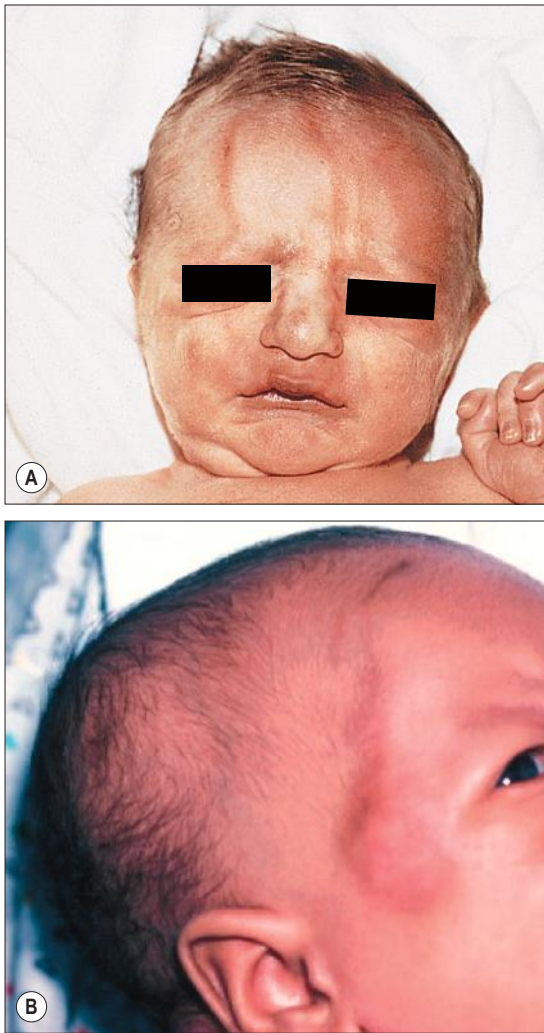


Figure 8.4 (A) Forceps marks over the face. (B) Forceps causing subcutaneous fat necrosis, an unusual association.

PETECHIAE AND ECCHYMOSES

Petechiae on the head, neck, and upper body are likely to be caused by pressure differences that occur during passage of the chest through the birth canal. It is important to exclude the possibility of an underlying infection or hematologic disorder with appropriate laboratory studies. Petechiae caused by trauma are innocuous and usually fade within 2–3 days.

Ecchymoses may be extensive following a traumatic or breech delivery. Large areas of bruising may result in hyperbilirubinemia, requiring phototherapy. Ecchymoses resolve gradually, but may take up to several days to disappear completely.

Caput succedaneum

Diffuse edematous swelling of the scalp, when it is the presenting part, is known as caput succedaneum. Extravasation of blood or serum above the periosteum occurs as a result of venous congestion caused by pressure of the uterus, cervix, and the vaginal wall on the infant's head during a prolonged or difficult labor and delivery. Because the accumulation of fluid is external to the periosteum, it crosses the midline and is not limited by the suture lines. If labor is prolonged, petechiae,

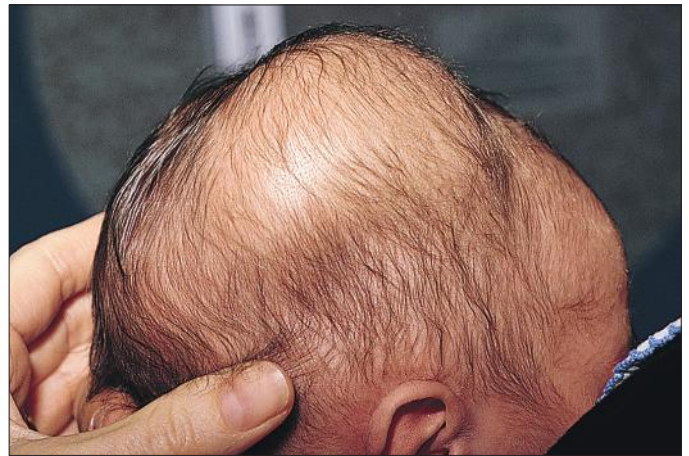


Figure 8.5 Unilateral cephalhematoma localized to the parietal bone.

purpura, and ecchymoses, as well as molding of the head and overriding sutures, may be prominent features. Unlike cephalhematoma, with which a caput is occasionally confused, the skin findings resolve within a few days. The molding may take a few weeks to disappear. Occasionally, if severe, tissue necrosis and a localized area of scarring alopecia may ensue.

Cephalhematoma

Cephalhematoma is caused by rupture of the emissary or diploic veins of the skull during a prolonged or difficult labor or delivery. The result of subperiosteal hemorrhage, it differs clinically from caput succedaneum in that it is almost always unilateral. The hematoma is localized most often to the area over the parietal bone, and the mass is confined by the periosteum, which adheres to the margin of the bone (Fig. 8.5). Cephalhematoma less frequently involves the occipital bones, and only rarely the frontal bones. If both parietal bones are involved, the hematomas are sharply demarcated and separated by a midline depression corresponding to the intervening suture. The overlying scalp is not discolored.

Cephalhematomas are seen more commonly in vacuum-assisted vaginal deliveries than in forceps or spontaneous births.^{17,18} The swelling may not become apparent until several hours to days after birth. As the hematoma ages, it develops a calcified rim and is gradually completely overlaid with bone. Estimates of underlying skull fractures have ranged from 5.4% to 25%.¹⁹ Differential diagnosis includes caput succedaneum and cranial meningocele.²⁰ Meningoceles can be differentiated by the presence of pulsations, increased pressure when crying, and the presence of a bony defect on X-rays. Infection of the mass and severe hemorrhage resulting in anemia and hyperbilirubinemia are rare complications for which antibiotics, blood transfusions, and phototherapy may be required.²¹ Treatment is unnecessary for uncomplicated lesions. Most cephalhematomas are resorbed during the first few weeks of life and are of no consequence.¹⁷ Occasionally, they calcify and persist for months to years.

Subgaleal hemorrhage

Subgaleal hemorrhage is a rare but potentially life-threatening complication that occurs when emissary veins are ruptured, most commonly by instrumentation at delivery. Like

cephalhematomas, vacuum-assisted delivery increases the incidence of subgaleal hemorrhage. Bleeding into the loose connective tissue of the subgaleal (also known as the subaponeurotic) space can be extensive, leading to severe anemia, disseminated intravascular coagulation (DIC) and hypovolemic shock.²² The area of swelling crosses suture lines and can extend from the brow line to the nape, as well as laterally to the temporal fascia located behind the ears.²³ Unlike cephalhematomas, which are limited by the periosteum and suture lines, the aponeurotic space may accommodate up to 260 mL of blood, approaching the circulating blood volume of a neonate, which is approximately 80 mL/kg. Physical assessment may reveal dependent swelling on the scalp that varies from firm to fluctuant, and fluid waves may be present when the area is palpated. The neonate may exhibit hypotonia, pallor and tachypnea. As hypovolemia worsens, signs of poor perfusion, tachycardia, oliguria, and eventually hypotension may ensue. The infant must be closely monitored for signs and symptoms of neurologic compromise, shock and bleeding. Treatment is aimed at maintaining normovolemia, and controlling coagulopathy.

Untoward effects of vacuum extraction

The formation of some type of hematoma is a common occurrence with the use of a vacuum extractor, although with the introduction of softer silicone cups, the risk has been reduced.²⁴ A 'chignon,' or artificial caput succedaneum, is created by adherence of the cup to the scalp and is most obvious immediately following removal of the cup. However, the swelling usually disperses relatively rapidly after birth. If a chignon is formed in the presence of a natural caput, the scalp may have a boggy sensation suggesting subgaleal hemorrhage (see above).²⁵

Cephalhematomas, a ring of suction blisters, lacerations, and abrasions may also result from the use of the vacuum extractor.²⁶ The latter are usually the result of prolonged traction and sudden detachment of the cup. Subcutaneous emphysema of the scalp has been attributed to vacuum extraction in an infant with a coexistent scalp electrode wound.²⁷ Cases of vesicular eruptions following vacuum extraction with or without the presence of herpes simplex virus (Fig. 8.6) have been reported, presumably from the combination of mechanical trauma and colonization.²⁸

Halo scalp ring

Alopecia in an annular configuration, presumably the consequence of localized injury during the birth process, has been



Figure 8.6 Vesicles related to vacuum extraction. (Courtesy of Warren Heymann, MD and Preston Chadwick, MD.)

referred to as 'halo scalp ring' injury.²⁹ Often – but not always – there is a history of a prolonged labor. The hair loss is manifest at birth, or shortly thereafter, as a band of alopecia ranging in width from 1 to 4 cm, usually located over the vertex (Fig. 8.7A). There is typically an associated caput succedaneum and in some instances, frank tissue necrosis (Fig. 8.7B). If the injury is mild, the alopecia is usually temporary;^{29,30} however, scarring alopecia may result if the injury is severe (Fig. 8.7C).^{31,32} The areas of scarring can often be corrected with plastic surgery. The presence of halo scalp ring implies soft-tissue hypoxia and as such, infants with this condition should be monitored for developmental defects, which could have accompanied prolonged labor and associated hypoxic states.

Lacerations

Scalpel lacerations to the infant during cesarean section represent a potential form of injury. Smith and coworkers³³ found an incidence of fetal injury of 1.9% in a series of 896 cesarean deliveries. Lacerations were much more common in those deliveries where the indication was nonvertex presentation (breech or transverse lie). In these infants, the injuries were almost always located on the lower portion of the body, whereas infants in a vertex presentation usually sustained their lacerations on the head. Failure to recognize the injury in the delivery room was a common occurrence.

Burns and thermal injury

CHEMICAL BURNS

Very low birthweight (VLBW), preterm infants are particularly predisposed to skin damage from topically applied chemicals and medications.³⁴ This is largely due to an immature epidermal barrier, and their vulnerability may be accentuated by hypoxia and hypothermia.

Chemical burns from concentrated disinfectants or other solvents have been reported following their use in the neonatal intensive care nursery (see Chapter 5). Burns are evident as intense erythema associated with blister formation and sloughing of the damaged skin (Fig. 8.8).

Isopropyl alcohol has caused second- and third-degree burns when substituted for electrode paste beneath electrocardiograph (ECG) leads or used as a preparation for the umbilical area. Alcohol-based skin cleansers, containing chlorhexidine gluconate (CHG), have also been reported to cause extensive burns in neonates (Fig. 8.9).^{35–37} Tissue damage can be prevented if the alcohol in the preparation is allowed to evaporate before draping for invasive procedures and carefully removed afterwards. Because of the reported incidence of CHG-related skin breakdown, use should be limited or avoided for VLBW infants.

THERMAL INJURY

Scald injury and contact burns must be considered in the differential diagnosis of bullous lesions of unknown etiology. Inadvertent immersion injury was described in one such instance where the temperature of the hospital water supply was raised for purposes of infection control.³⁸ Contact with a disposable warmer causing cicatricial alopecia and a cranial defect requiring bone grafts was reported in another neonate.³⁹ Reports of deep burn injuries with relatively low-temperature (42°C)



Figure 8.7 (A) Halo scalp ring: a band of alopecia resulting from localized injury during the birth process. (B) Halo scalp ring with tissue necrosis 1 week after birth. (C) Halo scalp ring healed with scarring alopecia. (A: Courtesy of John Hall, MD.)

warming bottles have also been reported in the neonatal period.^{40,41}

Burns related to attempts to warm hypothermic neonates with hot water-filled gloves or other items heated in a microwave have also been reported (Fig. 8.10).⁴² Scald burns become



Figure 8.8 Alcohol burn on a premature infant.



Figure 8.9 A periumbilical burn from 2% chlorhexidine gluconate and 70% isopropyl alcohol. The site was draped for insertion of an umbilical line leading to pooling of the preparation on the infant's skin.

a much more common issue in older infants with non-accidental injuries, e.g. being forced to be immersed in very hot bath water.

TRANSILLUMINATION BLISTERS

Thermal burns may occur as a complication of the use of transillumination devices for the detection of hydrocephalus, subdural effusions, cystic hygroma, pneumothorax, pneumomediastinum, or for localization of arteries and veins for blood sampling. Typical lesions are small (<5 mm), round, discrete blisters with a necrotic base that develop at sites of transillumination (Fig. 8.11).⁴³ It is thought that specific wavelengths of the high-intensity fiberoptic light are converted to heat energy in the skin, causing thermal damage. Infrared and ultraviolet filters within the light source, usually a quartz halogen lamp, eliminate wavelengths of <570 nm, reducing the risk of thermal injury. A defect in the transilluminator unit, missing filters,⁴⁴ prolonged contact with the skin or failure of the filter to function properly have accounted for the occurrence of these blisters in neonates.



Figure 8.10 Preterm infant with iatrogenic burn after gloves filled with hot water were placed on the skin in an attempt to warm the baby. (Courtesy of the S.T.A.B.L.E. Program, ©2013.)



Figure 8.11 Thermal burns from a transillumination unit causing blisters in a neonate. (Courtesy of Sheila Fallon-Friedlander, MD.)

SUBCUTANEOUS FAT NECROSIS ASSOCIATED WITH THERAPEUTIC HYPOTHERMIA

Therapeutic hypothermia has become the standard of care for treatment of hypoxic ischemic encephalopathy and has been shown to decrease mortality and reduce the incidence of long-term neurodevelopmental disability at 18–24 months' follow-up.⁴⁵ As a result, more tertiary neonatal units are utilizing this treatment modality and subcutaneous fat necrosis (SCFN) has been noted in some infants undergoing whole body cooling.^{45,46} SCFN can also be seen with perinatal hypoxia without therapeutic cooling,⁴⁷ so infants cooled have an additional risk factor for this condition. SCFN is discussed in greater detail in [Chapter 27](#).

Physical findings include firm nodules and plaques varying in color from flesh colored to erythematous, blue or purple.⁴⁵ For the infant on cooling therapy, the areas most affected are those in contact with the cooling blanket, including the back, shoulders, upper arms, thighs, and buttocks ([Fig. 8.12](#)).⁴⁶

Hypercalcemia occasionally complicates the course in these infants.⁴⁸ Rarely, there is accompanying soft tissue calcification



Figure 8.12 Subcutaneous fat necrosis from whole body cooling for hypoxic ischemic encephalopathy.



Figure 8.13 Neonate with erosions and ulcerations on the torso due to epidermal and dermal injury from 'dermal stripping'.

identifiable by biopsy or radiography.⁴⁹ The presence of soft tissue calcification does not seem to portend a more ominous prognosis and eventually resolves. Preventative care involves frequent assessment of the skin, positional changes and the use of pressure-relieving mattresses and pillows.

Mechanical injury

DERMAL STRIPPING

Application and removal of adhesives and dressings can lead to inadvertent removal of the stratum corneum, pain, inflammation, edema, disrupted barrier function and increased transepidermal water loss (TEWL).^{50,51} For the preterm infant, the bond between adhesives and epidermis may be stronger than the bond between epidermis and dermis, leading to extensive tissue loss with adhesive removal ([Figs 8.13, 8.14](#)).⁵¹

Pressure ulcers

Pressure ulcers are defined as a localized injury to the skin and/or underlying tissue, usually over a bony prominence, due to



Figure 8.14 Erosion of the abdominal skin from application and removal of adhesives.

pressure or pressure in combination with shear and/or friction (Fig. 8.15).⁵² The classification for pressure ulcers can be found on the National Pressure Ulcer Advisory Panel's (NPUAP) website.⁵³ The incidence of pressure ulcers has been reported to be as high as 23% in the neonatal intensive care unit (NICU) and 27% in the pediatric intensive care unit (PICU).⁵⁴ A more recent multisite study of nine PICUs, including 5346 patients, showed the aggregate incidence of pressure ulcers to be 10.2%. The study found risk factors for development of pressure ulcers to include: age <2 years; PICU stay of >4 days; and treatment including the use of BiPAP, CPAP, conventional mechanical ventilation, high frequency oscillatory ventilation (HFOV) and extracorporeal membrane oxygenation (ECMO) (Fig. 8.15A,B).⁵⁵ Neonates and infants with limited mobility, neuromuscular immaturity, hemodynamic instability, decreased sensory perception, and dependence on their caregivers for positional changes, are at increased risk of skin breakdown (Fig. 8.15C). Because of their disproportionately large head

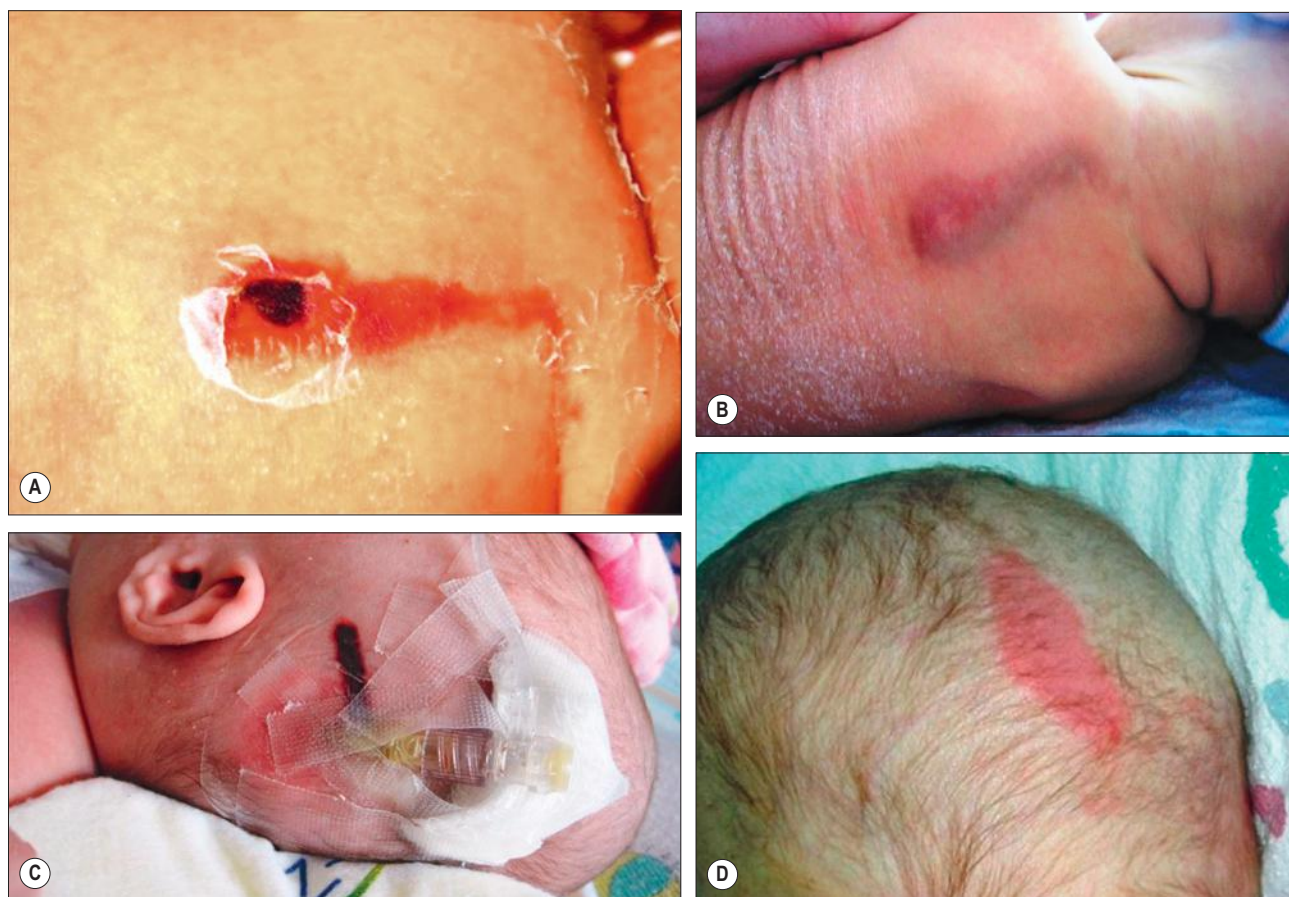


Figure 8.15 Pressure ulcers. (A) Unstageable pressure ulcer located along the spine of a neonate on ECMO. (B) Resulting scar from same pressure ulcer. (C) Suspected deep tissue injury discovered after a lengthy surgical case where the infant's head rested on the sliding clamp of an IV connector. (D) Stage I occipital pressure ulcer (nonblanching erythema) from immobility post-surgery. (D, Courtesy of Shelley Diane RN, MS, CNS.)

Continued



relative to body size, the most common site for pressure ulcer development in the infant is the occiput (Fig. 8.15D).^{54,56} Scarring alopecia of the occipital scalp has been documented as a consequence of ischemia and compromised oxygenation, or as a complication of extracorporeal membrane oxygenation (ECMO) therapy in neonates.⁵⁷ During a 6-month period, five infants in a neonatal ICU were observed to develop erythema and edema that progressed to crusted ulcerations (Fig. 8.15E) and resulted in a patch of scarring alopecia (Fig. 8.15F). The

ulcers were believed to be the result of prolonged pressure in a setting of hypoperfusion, acidosis, and hypoxemia. The institution of a protocol requiring frequent repositioning of the head and use of a temperature-stable gel pad as preventive measures, eliminated this problem.

For the VLBW infant, the combination of lengthy hospitalization, immature skin and dependence on medical devices increases the risk for pressure-related injury (Fig. 8.15G,H). Use of nasal continuous positive airway pressure (NCPAP) has been

correlated with development of pressure ulcers in the preterm infant (Fig. 8.15I). The greatest risk factors include gestational age <32 weeks; birthweight <1500 g; >5 days on NCPAP, and >14-day stay in the NICU.⁵⁸ Case reports of forehead pressure necrosis from the CPAP apparatus with resultant scarring and alopecia have also been published (Fig. 8.15J).⁵⁹

Use of a validated assessment tool such as the Braden Q Scale⁶⁰ can detect risk early. Use of support surfaces to minimize friction and shear, frequent repositioning and head to toe assessment (especially under medical devices) can aid in prevention of pressure ulcers for neonates and infants.^{55,61}

Umbilical artery catheterization

Umbilical arterial catheterization (UAC) is standard practice in the neonatal intensive care unit for monitoring intravascular pressures, chemistries, pH, and blood gases, and for administering fluids and medications to critically ill neonates. However, this procedure is fraught with risk of serious complications, even in experienced hands. Thrombosis is the most frequent problem, as documented by aortography. Other potential complications include vasospasm, blanching of the limbs (Fig. 8.16A), embolism, perforation of the vessels, vascular damage from hypertonic solutions, hemorrhage, infections, and ischemic (Fig. 8.16B) and chemical necrosis.⁶² These untoward events are usually caused by incorrect placement of the catheter, or to unduly rapid infusion of hazardous drugs or hypertonic solutions, rather than vessel injury.

Vasospasm may occur during placement of the catheter in the umbilical artery. It is manifest by temporary blanching or cyanosis of the leg and foot (Fig. 8.16C,D). Prompt removal of the catheter is indicated, and if this procedure is followed, sequelae are unlikely.

Thromboses and multiple small emboli can cause infarcts of the toes and lower extremities. Depending on the location of the thrombus, unilateral or bilateral gangrene of the feet, lower extremities, or buttocks can occur.^{62–64} Gangrene of the distal upper extremity with loss of fingers has also been documented secondary to similar events following percutaneous radial artery catheterization.⁶⁵ Early skin changes include erythema, transient blanching, vesicles, and bulla formation (Fig. 8.16E). These lesions may abate or may progress to extensive skin and subcutaneous tissue necrosis, demarcation, and gangrene (Fig. 8.16F).⁶⁴

Perinatal gangrene of the buttock

This alarming and fortunately rare occurrence is usually attributed to iatrogenic causes⁶⁶ but has also been documented as an apparently spontaneous event.^{67,68} The onset is heralded by the sudden appearance of an erythematous patch involving the buttock, perineum, and genitalia. Within hours, the involved area rapidly becomes edematous and then rock hard and cold to the touch, with well-defined black borders. Bullae may form on the surface. Generally, the lower limbs are spared and remain warm and normal in color, with palpable femoral pulses. Over the subsequent several days, the necrotic tissue demarcates and sloughs, leaving a deep ulcer that heals by secondary intention with scarring.

The diagnosis is made on the basis of the abrupt onset and clinical findings. The differential diagnosis is mainly that of an

infectious process, but cultures are invariably negative, as are biochemical and hematologic laboratory studies. Chemical or thermal injury must also be considered.

The presumed cause is an occlusive vascular event involving the internal iliac artery. This artery, which feeds into the umbilical artery, splits into two terminal branches, the inferior gluteal and the internal pudendal arteries; these two vessels supply the buttock, perineum, vulva, and scrotum. Vasospasm followed by thrombus formation resulting from a variety of factors, such as injury to the umbilical cord or obstruction by a misdirected umbilical catheter, may result in this condition. Despite the extent of the gangrene, affected skin usually heals without complications and the sphincters remain intact.^{66,67}

Complications of phototherapy

Visible light phototherapy has become standard therapy in the newborn nursery for infants with significant indirect hyperbilirubinemia. Visible light energy isomerizes unconjugated bilirubin to more polar forms, which are excreted into the bile and ultimately into the stool within minutes of exposure. Bilirubin absorbs light maximally in the blue portion of the spectrum (420–520 nm). Blue, green and turquoise light are considered the most effective at reducing bilirubin. Light emitting diodes (LEDs) are a newer form of therapy that provides high irradiance without concern for heat-related side-effects. The blue hue emitted from this type of unit has been reported to cause visual disturbances and dizziness for staff members, so amber LEDs have been added to avoid this side-effect without affecting irradiance. Other available delivery systems include halogen spotlights which can generate heat, therefore cannot be placed closer to the infant than manufacturer recommendations, and fluorescent tubes in the form of bank lights and fiberoptic blankets.⁶⁹

Adverse effects of phototherapy are uncommon, but include erythematous, purpuric, and vesicular transient eruptions (see Chapters 5 and 20), and bronze baby syndrome (see below and Fig. 8.20).

PHOTOTHERAPY-INDUCED DRUG ERUPTIONS

Erythematous and vesiculobullous eruptions may be associated with phototherapy under other circumstances. Drug-induced phototoxicity eruptions have been documented in neonates receiving certain therapeutic agents (e.g., furosemide or fluorescein dye for a radiologic procedure) or exposed to methylene blue dye prenatally.^{70–72} These eruptions have occurred in infants given a photosensitizing drug and exposed to light of the appropriate wavelength to cause photoactivation of the chemical compound. As with true burns, these bullae develop only on light-exposed skin. Discontinuation of therapy usually results in an uneventful recovery.

TRANSIENT PORPHYRINEMIA AND PHOTOTHERAPY ERUPTIONS

Transient porphyria in combination with phototherapy has also been documented as a cause of blisters and erosions,⁷³ as well as erythematous and purpuric lesions^{74,75} in several neonates with hemolytic disease (Fig. 8.17). The eruptions in all cases were confined to exposed areas, sparing the sites protected from the lights (e.g. skin under leads, dressings, and



Figure 8.16 (A) Blanching of lower extremities from umbilical arterial catheterization. (B) Vascular compromise of the buttocks. (C) Blanched toes from arterial spasm with presence of UAC. (D) Purplish discoloration from microemboli. (E) Early skin changes of reticulated erythema resulting from attempted umbilical artery catheterization. (F) Gangrene of the foot secondary to umbilical artery catheterization and thrombosis. (A,B,C: Courtesy of the S.T.A.B.L.E. Program, ©2013.)

temperature probes). Onset is typically between 1 and 4 days after initiation of phototherapy, but occasionally delayed.⁷³ Reactions include violaceous discoloration resembling sunburn,⁷⁴ purpura,⁷⁵ and least commonly, erosions and skin fragility.⁷³

Skin biopsy specimens from purpuric lesions show only extravasation of erythrocytes⁷⁵ without epidermal changes, thus

distinguishing the eruption from a burn. The porphyrin levels in affected infants vary but can include elevated free erythrocyte protoporphyrin and zinc protoporphyrin levels,⁷⁴ and increased levels of both plasma coproporphyrin and protoporphyrins.^{73,75} The cause of elevated porphyrin levels in these infants is postulated to be due to multiple factors, including cholestasis, altered hepatic function, concomitant administration of

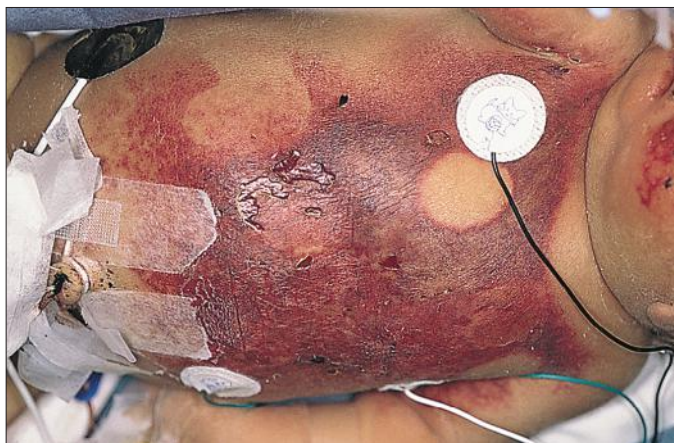


Figure 8.17 Photosensitive eruption in a neonate with transient porphyria associated with hemolytic disease of the newborn. (Courtesy of Julie Prendiville, MD.)

photosensitizing drugs, blood products, or renal failure. The differential diagnosis includes true porphyria, infections, epidermolysis bullosa, neonatal lupus erythematosus, metabolic photosensitivity eruptions, and drug eruptions. Both the cutaneous eruption and the transient porphyria clear spontaneously within a few weeks, without significant sequelae.

BRONZE BABY SYNDROME

In this rare complication of phototherapy, occurring exclusively in infants with cholestatic jaundice, the infant's skin, serum, and urine become a gray-brown color after several hours under the phototherapy lamps (Fig. 8.18).⁷⁶ All affected infants have had prior evidence of hepatic dysfunction, marked by conjugated hyperbilirubinemia and retention of bile acids.⁷⁷ The serum acquires a dark brown color and shows a nonspecific absorbance from 380 to 520 nm on spectroanalysis.⁷⁷ The peculiar color has been attributed to the formation of a photo-oxidation product of bilirubin or to copper-bound porphyrins, which yield brown photoproducts in the presence of bilirubin.⁷⁸ It has also been suggested that biliverdin pigments may contribute to the bronzing effect.⁷⁹ The odd hue is easily distinguished from that of cyanosis or typical neonatal jaundice. The discoloration fades over time after phototherapy is discontinued, and there are no significant sequelae.

Calcinosis cutis

Calcification of the skin occurs as a consequence of deposition of hydroxyapatite crystals and amorphous calcium phosphate in the soft tissues. Based on the pathophysiologic mechanisms, calcinosis cutis is usually classified as *idiopathic* (normal tissue and a normal calcium/phosphorus ratio); *dystrophic* (damaged tissue and a normal calcium/phosphorus ratio); or *metastatic* (normal tissue and an abnormal calcium/phosphorus ratio). Iatrogenic calcinosis cutis in neonates is usually of the dystrophic type and is most often the result of an intravenous infusion of calcium gluconate or calcium chloride for treatment of neonatal hypocalcemia.^{80–82} It may also occur following the application of electrode paste containing calcium chloride for



Figure 8.18 Infant with bronze baby syndrome. (Courtesy of Walter Burgdorf, MD.)

electroencephalography, electromyography, or brainstem auditory evoked potentials, particularly if applied to abraded skin,⁸³ in association with subcutaneous fat necrosis, or as a result of repeated trauma from heel-sticks.

CALCINOSIS CUTIS FROM INFUSION OF CALCIUM SALTS

Visible evidence of soft tissue calcification develops on average 13 days after infusion of the calcium solution, with a range of 2 h to 24 days (Fig. 8.19). There may be marked swelling with an intense inflammatory response, even in the absence of extravasation of fluid, and occasionally, soft tissue necrosis. The calcification may take the form of papules, nodules, an annular plaque, a large subcutaneous plaque, or may have a linear configuration conforming to the vein in which the solution is administered. Lesions are firm, erythematous, and brown, yellow, or white; when extravasation has occurred they may be tender, warm, and fluctuant, resembling an abscess.⁸⁰

Radiographic changes can be detected as early as 4–5 days following the infusion.⁸¹ Three radiologic patterns have been described: (1) a calcified mass localized to or near the site of injection; (2) more diffuse calcification along fascial planes; and (3) a pattern of vascular or perivascular calcification.^{81,84}

The diagnosis of calcinosis cutis can be made clinically, based on the distinctive appearance of the skin lesions and confirmed by skin biopsy and/or radiographs. Differential diagnosis includes cellulitis, osteomyelitis, periostitis, hematoma, abscess, and subcutaneous fat necrosis.

Treatment is generally symptomatic, and spontaneous resolution occurs over several months by transepidermal elimination of the calcified material. An animal study has suggested that intralesional injection of triamcinolone may be effective in reducing inflammation and facilitating the resorption of calcium.⁸⁵

CALCIFIED NODULES OF THE HEELS

These lesions have been seen in association with blood sampling from the heel, principally in infants of low birthweight and



Figure 8.19 Calcified plaque on the forehead secondary to extravasation of calcium gluconate.



Figure 8.20 Calcified nodules on the heel secondary to heel-sticks.



Figure 8.21 (A) IV infiltration of normal saline. (B) Blood infiltration.

young gestational age, who as neonates received numerous heel-sticks in the nursery.⁸⁶ Rho and colleagues,⁸⁷ however, reported a calcified heel nodule after a single heel-stick. Onset is usually between 4 and 12 months after birth and is marked by the appearance of multiple tiny white or yellow specks within depressed areas on the heels (Fig. 8.20). The papules may enlarge and become elevated and firm, but are usually not inflamed or symptomatic.

Infiltration and extravasation injuries

Neonates and infants with peripheral intravascular catheters (PIVs) and peripherally inserted central catheters (PICC lines) are wholly dependent on their caregivers to continuously monitor the sites to prevent complications. This population is at high risk for infiltration and extravasation injury secondary to their inability to verbalize pain and due to the fragility of their veins.⁸⁸ Infiltration is defined as the inadvertent leakage of

a non-vesicant into surrounding tissue, for example, isotonic fluids such as 5% dextrose, normal saline and blood (Fig. 8.21). Extravasation involves leakage of a vesicant into surrounding tissue, for example, amino acid solutions, calcium salts, and vasopressors. Extravasation of intravenous fluids and medications into subcutaneous tissue can lead to tissue necrosis and scar formation, particularly in premature infants who have fragile skin and minimal subcutaneous tissue.

The prevalence of extravasation injuries in neonatal intensive care units in the UK has been estimated to be 38 per 1000 babies, with 70% of injuries occurring in infants of 26 weeks' gestation or less.⁸⁹ The majority of extravasation injuries occur with peripheral catheters, with extent of damage dependent on the volume and physicochemical characteristics of the infiltrated solution.⁹⁰ Extravasation injuries are usually characterized by pain and swelling near the intravenous site, which may progress to blanching, signs of impaired perfusion, blistering, discoloration, ulceration, and eschar formation (Fig. 8.22), or

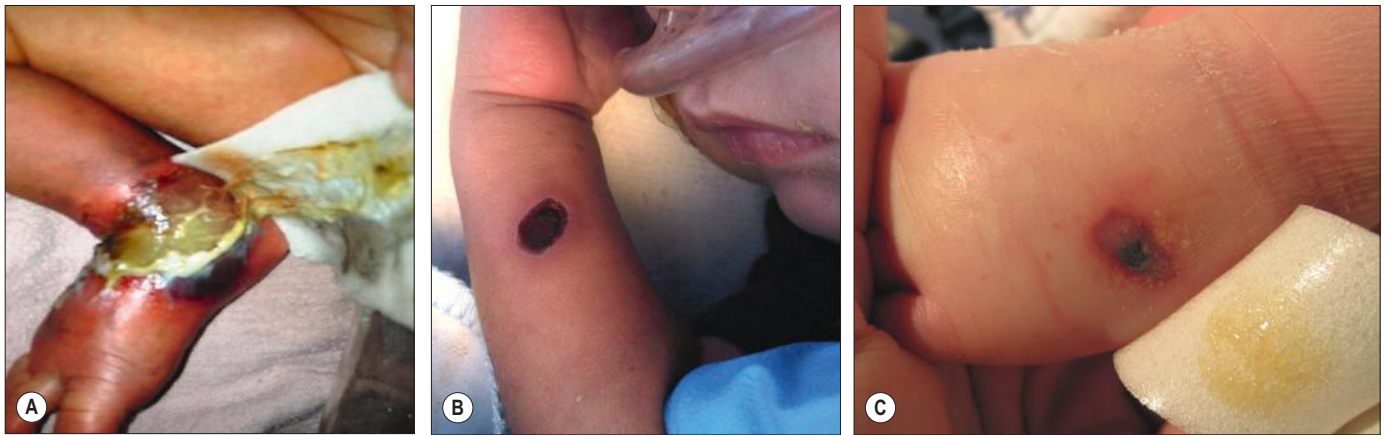


Figure 8.22 (A) Extravasation of dopamine hydrochloride. (B) Eschar formation after extravasation of nafcillin. (C) Extravasation of ammonium chloride.

with calcinosis cutis after infiltration of calcium solutions (see above). Scar formation is related to the degree of tissue damage and can result in either aesthetic or functional impact. Over time, the scarring may improve.¹⁶

There is no consensus on treatment for extravasation injuries in neonates. Elevation, multiple puncture technique, saline flushing, liposuction, phentolamine and hyaluronidase have been reported to be helpful, although further studies are needed in neonates.^{90–92} Wound care with hydrocolloid or hydrogel dressings may promote healing and help to minimize scar formation. Prevention of extravasation injury requires frequent monitoring,⁹³ securing IVs to allow visualization and stabilization of the site, and the use of central venous access for administration of potentially irritating fluids and medications.^{88,92}

Phlebitis

Phlebitis, while rare in neonates and infants, can occur with resultant erythema, swelling, pain, warmth and a palpable cord.⁹⁴ Chemical, mechanical and bacterial factors may contribute to development of phlebitis (Fig. 8.23). Use of central lines for administration of caustic or irritating medications can lower incidence of chemical phlebitis. PICC lines are a common type of vascular access for ill newborns and infants. Phlebitis is one potential complication. Measures to ensure strict hand hygiene, skin antisepsis and aseptic catheter maintenance can minimize bacterial phlebitis. Selection of the smallest catheter relative to vessel size can decrease mechanical irritation to the intima, as can careful securement of IVs in areas of flexion with the use of armboards and securement devices to prevent ‘movement’ of the IV.⁹²

Complications of monitoring

The use of noninvasive techniques for skin surface monitoring of blood gases and temperature has become routine practice in the newborn intensive care nursery.⁹⁵ Transcutaneous measurements of oxygen and carbon dioxide tension and pulse oximetry for assessment of arterial saturation levels provide accurate, reproducible information facilitating clinical management of premature and sick infants. Although these techniques are widely used, they do pose some risk of damage to the infant’s skin at sites of contact with the sensors and electrodes.



Figure 8.23 Bacterial phlebitis.

ANETODERMA OF PREMATURITY

This entity consists of atrophic patches of skin as a sequelae of extreme prematurity (24–29 weeks) or low birthweight and lengthy stays in a neonatal intensive care unit.^{96,97} Characteristic skin lesions are absent at birth and lack an identifiable antecedent inflammatory phase, typically being noticed between 6 weeks and 10 months of age. The patches are usually confined to the anterior trunk and proximal limbs, are oval or circular, appear depressed, and measure a few millimeters to several centimeters in diameter (Fig. 8.24). They often develop at sites of application of adhesives and placement of monitoring devices. Histopathologic examination of a skin biopsy specimen demonstrates a reduction or absence of dermal elastic tissue.⁹⁶

It has been postulated that the condition is a result of a subclinical inflammatory reaction to trauma or a transient metabolic derangement in the skin. These scars persist, though they may become less noticeable over time.

PULSE OXIMETRY

Pulse oximetry relies on the spectrophotometric analysis of light to measure the oxygen saturation of hemoglobin. The technique employs a sensor that wraps around a hand, foot, or finger, or an ear probe that clips to the antihelix. It requires no calibration and no skin heating and provides almost continuous measurement of oxygen saturation. Tight application of a probe can result in skin erosion, hyperpigmentation, blister, or pressure necrosis.⁹⁸ Because pulse oximetry does not require tight contact with the skin, this complication is avoidable by frequent inspection, avoidance of tourniquet type fit and rotation of the probe site.⁹⁸

TRANSCUTANEOUS OXYGEN MONITORING

Although also considered a noninvasive procedure, transcutaneous oxygen monitoring poses a greater risk for local skin damage because the electrode must be heated to 42–45°C to promote adequate blood flow.^{95,99,100} Thermal injury is a relatively frequent problem and is directly related to the temperature of the sensor, the sensitivity of the infant's skin, and the duration of placement of the monitoring device at a single skin site. First-degree burns are common, although the erythema is likely to fade by 12 h (Fig. 8.25).⁹⁹ A smaller number of infants, more often those born prematurely, sustain a more severe thermal reaction such as a second or even third degree burn.⁹⁹ Pulse oximetry is now widely used, decreasing iatrogenic burns from transcutaneous oxygen monitoring.

TRANSCUTANEOUS CARBON DIOXIDE MONITORING

Transcutaneous carbon dioxide monitoring (TCO₂) is a non-invasive method of measuring carbon dioxide in the NICU. This form of monitoring involves application of a probe that heats the skin to 42–45°C. Isolated cases of burns, especially in the preterm population,¹⁰¹ have been reported. Therefore, careful assessment and rotation of sites is recommended.



Figure 8.24 Area of anetoderma noted at several months of age in an infant born prematurely.

Meatal ulceration following circumcision

Mackenzie¹⁰² has proposed that meatal ulceration is a frequently unrecognized consequence of neonatal circumcision. He has suggested that removal of the prepuce subjects the epithelium of the glans penis to undue irritation from the diaper, which may result in erosions followed by healing with stenosis. Because the erosions do not necessarily occur in the immediate postoperative period, the cause-and-effect relationship is not appreciated. Other rare complications include direct injury to the glans and urethra, bleeding, and infection.

Cutaneous necrosis following suture ligation of supernumerary digits and accessory tragi

Supernumerary digits and accessory tragi (which may erroneously be referred to as 'tags') are sometimes removed with suture ligation rather than surgical excision. This method, by its nature, constricts the blood flow to the skin and leads to skin necrosis. If the appendage is not tiny, the amount of necrosis can be considerable (Fig. 8.26) and can even serve as a potential nidus for infection. Accessory tragi have associated cartilage and for this reason, are not well-suited to this technique.¹⁰³ Supernumerary digits treated with suture ligation can also result in traumatic neuroma and chronic pain.¹⁰⁴

Auriculotemporal nerve syndrome

Auriculotemporal nerve (Frey) syndrome is characterized by unilateral flushing and sweating in the distribution of the auriculotemporal nerve (lateral cheek, medial ear, and frontotemporal scalp) in response to gustatory stimuli. In children, it is usually a consequence of perinatal birth trauma to the parotid region, especially associated with forceps delivery.¹⁰⁵ When the auriculotemporal nerve is damaged, regenerating parasympathetic nerve fibers intended for the parotid may be misdirected



Figure 8.25 Multiple first-degree burns from transcutaneous oxygen monitoring device.



Figure 8.26 Necrosis of a supernumerary digit after suture ligation.

and anastomose with the sympathetic nerve fibers innervating the sweat glands and small blood vessels. Frey syndrome usually presents around the time of introduction of solid foods as chewing elicits a stronger stimulation of the parotid gland than does sucking of formula or breast milk.¹⁰⁶ Erythema and flushing typically begins shortly after mastication, and lasts 15–45 min. Unlike adults, sweating is uncommon in children with Frey syndrome, possibly due to immaturity of the eccrine sweat glands. Bilateral involvement has been reported, but is uncommon.¹⁰⁷ Treatment is usually not necessary in children, as spontaneous resolution does occur within a few years.¹⁰⁶

Horner syndrome

Horner syndrome is characterized by hemifacial anhidrosis and flushing with ipsilateral miosis, mild ptosis, apparent enophthalmos with slight elevation of the lower eyelid, and iris hypochromia.¹⁰⁸ It is secondary to damage to the sympathetic nerves on the ipsilateral side to the defects. In infants and children, Horner syndrome can be caused by birth trauma with brachial plexus injury, neuroblastoma, vertebral abnormalities, thoracic surgery, and carotid artery thrombosis;¹⁰⁹ however, George and colleagues reported no identifiable cause in 70% of 23 infants with Horner syndrome.¹¹⁰

Linear bands of infancy

Linear bands of infancy (raised limb bands) is an uncommon entity which was first described in 2002 by Meggitt and coworkers.¹¹¹ There have been limited cases described since then, although this is likely due to under-reporting.^{112–116} Most cases present in the first 1–4 months of life with linear, flesh colored to reddish-brown or hyperpigmented patches or plaques, which can be circumferential or near-circumferential on the extremities (Fig. 8.27). They are most commonly found on the lower legs but can be seen on the arms as well. Unfortunately, the lesions are often persistent but can improve with time. The



Figure 8.27 Linear reddish-brown patches on bilateral lower extremities. (Courtesy of Liborka Kos, MD.)

etiology is unclear, although it has been speculated that linear bands are related to constriction bands. They have been associated with both prematurity and amniotic bands in several of the reported cases, although the cases associated with amniotic bands were much more extensive.¹¹² More recently, it has been postulated that the linear bands may be associated with mast cell activation and subsequent tissue fibrosis after local pressure, as there is often a history of the lesions forming after contact with elasticized sock tops.¹¹⁵ There has been one report of complete resolution of the linear bands after application of olopatadine hydrochloride, a topical antihistamine ophthalmic solution.¹¹⁶

Cutaneous vaccination reactions

Cutaneous reactions to vaccinations in infants are not infrequent. Injection site reactions are most common (19%) with rash occurring in 8% of children.¹¹⁷ Injection site reactions can vary from mild erythema and/or swelling at the injection site to extensive swelling along limbs, occasionally involving adjacent joints.¹¹⁸ There are many other cutaneous reactions reported in the literature that can occur in association with vaccinations, including Gianotti Crosti-like eruptions, Henoch Schönlein purpura, serum sickness-like reaction, pseudolymphoma, lichen striatus, psoriasis, lichen planus, granuloma annulare, erythema multiforme, anetoderma, morphea, mastocytomas, and incontinentia pigmenti reactivation. BCG vaccinations have specific associated reactions in addition to the expected typical scar formation at the vaccination site including vaccine granulomas and tuberculid-like reactions.

Kemmeren and colleagues reported 1162 cases of 'discolored leg syndrome' in infants after vaccinations.¹¹⁹ They estimated the incidence to be 58 per 100 000 children vaccinated in their European population. The clinical presentation varies from patchy red, blue, or purple discoloration of the leg and/or petechiae with or without swelling. Onset typically occurs within 4 h of vaccination and resolves within 12 h. Bilateral lower extremity involvement is most common, although homolateral and even contralateral involvement can occur. Discolored leg syndrome is often accompanied by fierce crying and, less commonly, pallor and cyanosis. Pathophysiology is unknown, but it is thought to be a vasomotor reaction.

Nicolau syndrome (embolia cutis medicamentosa) is very rare; however, nine cases have been reported in children related to vaccinations.^{120–122} It is a consequence of accidental intravascular or perivascular drug injection, with subsequent arterial embolism. It is characterized by the sudden onset of painful swelling, livedoid erythema, hemorrhagic patches or bullae, followed by necrosis of the skin, subcutaneous fat, and occasionally muscular tissue. Lipoatrophy secondary to inadvertent administration of diphtheria/tetanus/pertussis (DTP) vaccinations into the subcutaneous tissue has also been reported.¹²³

Non-accidental trauma

Both accidental and non-accidental trauma are unfortunately common in infants and toddlers. It is important to recognize signs of non-accidental trauma early, as approximately 50% of children who have been abused are at risk of subsequent injury and 10% are at risk of death.^{124,125} Up to 90% of victims of physical abuse present with skin findings.¹²⁶ Cutaneous manifestations of abuse can be distinctive and distinguishable from accidental trauma, although this distinction can be difficult and other clues are often needed. Red flags in the history include vague explanations of injury, history that changes with time, delay in seeking medical care, repeated emergency room visits or repeated injuries/fractures, history inconsistent with the physical findings, and inappropriate developmental stage of the child for the injury to be plausibly accidental.¹²⁶

Cutaneous manifestations of physical abuse include bruises, lacerations, abrasions, burns, oral trauma, bite marks, and traumatic alopecia. Accidental bruising is most common over the knees and anterior tibial area (Fig. 8.28), but can occur over any bony prominence. Bruising on relatively protected sites (upper arms, medial and posterior thighs, hands, trunk, cheeks, ears, neck, genitalia, buttocks) should raise suspicion of abuse.¹²⁶ Bruising is very rare in infants <6 months of age, as they are not yet mobile and should also raise concern for abuse. Pattern bruising, including linear or circumferential bruises, loop marks, finger marks, or bruises in the shape of an object, is a strong indicator of abuse. Human bite marks are usually circular or oval and are often superficial causing only bruising.

Inflicted burns are more common in children under 3 years old, and scalds are the most frequent form of burn abuse.^{127,128} Forced immersion burns are symmetrical and have clear lines of demarcation with uniform burn depth, whereas accidental immersion burns have irregular borders, nonuniform depth, and splash marks. Inflicted scald burns usually involve the buttocks, perineum, and lower extremities and include stocking and glove distribution, zebra stripes, and donut hole sparing. Stocking and glove burns occur with forcible immersion of hands and/or feet in hot water, resulting in symmetrical, circumferential, well-demarcated burns. Zebra stripes are caused by sparing of the flexural creases when the body is immersed in hot water in a flexed position. Donut-hole sparing occurs when the buttocks are pressed against the bathtub which is relatively cooler than the water in it. Patterned contact burns in the form of objects are also highly suspicious of abuse. Cigarette burns are common and are characterized by well-demarcated 7–10 mm burns with a deep central ulceration. They are most common on the face, hands, and feet.

Petechiae over the head and neck can be a sign of attempted strangulation or holding an infant's neck while shaking. In infants, subtle injuries may be the only clue to serious internal



Figure 8.28 Typical bruising over the knees and pretibial surfaces related to accidental trauma.



Figure 8.29 Hyperpigmented patches of phytophotodermatitis. (Courtesy of Liborka Kos, MD.)

injury; therefore, it may be necessary to rule out associated head or abdominal trauma with CT or MRI.¹³⁰ Skeletal survey is necessary in all cases of suspected abuse in children younger than 2 years old.

Reporting suspected abuse is mandatory, and involving professionals experienced in the maltreatment of children is

crucial. The differential diagnosis of suspected child abuse is broad. Mongolian spots, leukemia cutis, neuroblastoma, hemorrhagic edema of infancy, coagulation disorders, lichen sclerosis with purpura, and coining can all be mistaken for bruising. Bullous impetigo, erysipelas, ecthyma, *Staphylococcal* scalded

skin syndrome, contact dermatitis, phytophotodermatitis (Fig. 8.29), epidermolysis bullosa, incontinentia pigmenti, and laxative ingestion can be confused with burns.

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KEY REFERENCES

23. Davis DJ. Neonatal subgaleal hemorrhage: diagnosis and management. *CMAJ* 2001; 164(10):1452–3.
24. Vacca A. Birth by vacuum extraction: Neonatal outcome. *J Paediatr Child Health* 1996;32: 204–6.
34. Kalia YN, Nonato LB, Lund CH, et al. Development of skin barrier function in premature infants. *J Invest Dermatol* 1998;111(2):320–6.
45. Hogeling M, Meddles K, Berk DR, et al. Extensive subcutaneous fat necrosis of the newborn associated with therapeutic hypothermia. *Pediatr Dermatol* 2012;29(1):59–63.
50. Cutting KF. Impact of adhesive surgical tape and wound dressings on the skin, with reference to skin stripping. *J Wound Care* 2008; 17(4):157–8, 160–2.
54. Curley MA, Quigley SM, Lin M. Pressure ulcers in pediatric intensive care: incidence and associated factors. *Pediatr Crit Care Med* 2003; 4(3):284–90.
62. Cutler VE, Stretcher GS. Cutaneous complications of central umbilical artery catheterization. *Arch Dermatol* 1977;113:61–3.
66. Rudolph N, Wang HH, Dragutsky D. Gangrene of the buttock: A complication of umbilical artery catheterization. *Pediatrics* 1974;53: 106–9.
73. Mallon E, Wojnarowska F, Hope P, et al. Neonatal bullous eruption as a result of transient porphyria in a premature infant with hemolytic disease of the newborn. *J Am Acad Dermatol* 1995;33:333–6.
104. Leber GE, Gosain AK. Surgical excision of pedunculated supernumerary digits prevents traumatic amputation neuromas. *Pediatr Dermatol* 2003;20:108–12.

REFERENCES

- Jauniaux E, Rodeck C. Use, risks and complications of amniocentesis and chorionic villous sampling for prenatal diagnosis in early pregnancy. *Early Pregnancy Biol Med* 1995;1: 245–52.
- Cambiaghi S, Restano L, Cavalli R, et al. Skin dimpling as a consequence of amniocentesis. *J Am Acad Dermatol* 1998;39:888–90.
- Stoler JM, McGuirk CK, Lieberman E, et al. Malformations reported in chorionic villus sampling exposed children: A review and analytic synthesis of the literature. *Genet Med* 1999;1:315–22.
- Froster UG. Limb defects and chorionic villus sampling: results from an international registry, 1992–1994. *Lancet* 1996;347:489–1494.
- Golden CM, Ryan LM, Homes LB. Chorionic villus sampling: a distinctive teratogenic effect on fingers? *Birth Defects Res A Clin Mol Teratol* 2003;67:557–62.
- Ashkenazi S, Metzker A, Merlob P, et al. Scalp changes after fetal monitoring. *Arch Dis Child* 1985;60:267–9.
- Amann ST, Fagnant RJ, Chartrand SA, et al. Herpes simplex infection associated with short-term use of a fetal scalp electrode. *J Reprod Med* 1992;37:372–4.
- Okada DM, Chow AW, Bruce VT. Neonatal scalp abscess and fetal monitoring: Factors associated with infection. *Am J Obstet Gynecol* 1977;129:185–9.
- Wagener MM, Rycheck RR, Yee RB, et al. Septic dermatitis of the neonatal scalp and maternal endomyometritis with intrapartum internal fetal monitoring. *Pediatrics* 1984;74:81–5.
- Weiner EJ, McIntosh MS, Joseph MM, et al. Neonatal scalp abscess: is it a benign disease? *J Emerg Med* 2011;40(5):e97–101.
- Cordero L, Anderson CW, Zuspan FP. Scalp abscess: A benign and infrequent complication of fetal monitoring. *Am J Obstet Gynecol* 1983;146:126–30.
- Brook I, Frazier EH. Microbiology of scalp abscess in newborns. *Pediatr Infect Dis J* 1992; 11:766–8.
- Andrews WW, Schelonka R, Waites K, et al. Genital tract methicillin-resistant *Staphylococcus aureus*: risk of vertical transmission in pregnant women. *Obstet Gynecol* 2008; 111(1):113–18.
- Katz M, Greco A, Antony L, et al. Neonatal herpesvirus sepsis following internal monitoring. *Int J Gynecol Obstet* 1980;17: 631–3.
- Goldkrand JW. Intrapartum inoculation of herpes simplex virus by fetal scalp electrode. *Obstet Gynecol* 1982;59:263–5.
- Fox PE, Rutter N. The childhood scars of newborn intensive care. *Early Hum Dev* 1998; 51:171–7.
- Bofill JA, Rust OA, Davidas M, et al. Neonatal cephalohematoma from vacuum extraction. *J Reprod Med* 1997;42:565–9.
- Johnson JH, Figueroa R, Garry D, et al. Immediate maternal and neonatal effects of forceps and vacuum-assisted deliveries. *Obstet Gynecol* 2004;103:513–18.
- Zelson C, Lee SJ, Pearl M. The incidence of skull fractures underlying cephalohematomas in newborn infants. *J Pediatr* 1974;85:371–3.
- Winter TC, Mack LA, Cyr DR. Prenatal sonographic diagnosis of scalp edema/cephalohematoma mimicking an encephalocele. *Am J Roentgenol* 1993;161:1247–8.
- Tan KL, Lim GC. Phototherapy for neonatal jaundice in infants with cephalohematomas. *Clin Pediatr* 1995;34:7–11.
- Reid J. Neonatal subgaleal hemorrhage. *Neonatal Netw* 2007;26(4):219–27.
- Davis DJ. Neonatal subgaleal hemorrhage: diagnosis and management. *CMAJ* 2001; 164(10):1452–3.
- Vacca A. Birth by vacuum extraction: Neonatal outcome. *J Paediatr Child Health* 1996;32: 204–6.
- Benaron DA. Subgaleal hematoma causing hypovolemic shock during delivery after failed vacuum extraction: A case report. *J Perinatol* 1993;13:228–31.
- Metzker A, Brenner S, Merlob P. Iatrogenic cutaneous injuries in the neonate. *Arch Dermatol* 1999;135:697–703.
- Birenbaum E, Robinson G, Mashlach S, et al. Skull subcutaneous emphysema – a rare complication of vacuum extraction and scalp electrode. *Eur J Obstet Gynecol Reprod Biol* 1986; 22:257–60.
- Chadwick PW, Heymann WR. Vesicular eruption of vacuum-assisted delivery. *Pediatr Dermatol* 2012;Dec 28, doi 10.1111/pde.12070.
- Goujon E, Beer F, Gay S, et al. Anetoderma of prematurity: an iatrogenic consequence of neonatal intensive care. *Arch Dermatol* 2010; 146(5):565–7.
- Neal PR, Merk PF, Norins AL. Halo scalp ring: A form of localized scalp injury associated with caput succedaneum. *Pediatr Dermatol* 1984;2: 52–4.
- Tanzi EL, Hornung RL, Silverberg NB. Halo scalp ring: a case series and review of the literature. *Arch Pediatr Adolesc Med* 2002;156: 188–90.
- Prendiville JS, Esterly NB. Halo scalp ring: A cause of scarring alopecia. *Arch Dermatol* 1987;123:992–3.
- Smith JE, Hernandez C, Wax JR. Fetal laceration injury at cesarean delivery. *Obstet Gynecol* 1997;90:344–6.
- Kalia YN, Nonato LB, Lund CH, et al. Development of skin barrier function in premature infants. *J Invest Dermatol* 1998;111(2):320–6.
- Watkins AM, Keogh EJ. Alcohol burns in the neonate. *J Paediatr Child Health* 1992;28: 306–8.
- Reynolds PR, Banerjee S, Meek JH. Alcohol burns in extremely low birthweight infants: still occurring. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F10.
- Lashkari HP, Chow P, Godambe S. Aqueous 2% chlorhexidine-induced chemical burns in an extremely premature infant. *Arch Dis Child Fetal Neonatal Ed* 2012;97(1):F64.
- Mirowski GW, Frieden IJ, Miller C. Iatrogenic scald burn: a consequence of institutional infection control measures. *Pediatrics* 1996;98: 963–5.
- Matsumura H, Shigehara K, Ueno T, et al. Cranial defect and decrease in cerebral blood flow resulting from deep contact burn of the scalp in the neonatal period. *Burns* 1996;22: 560–5.
- Mohrenschlager M, Weigl LB, Haug S, et al. Iatrogenic burns by warming bottles in the neonatal period. *J Burn Care Rehab* 2003;24: 52–5.
- Rimdeika R, Bagdonas R. Major full thickness skin burn injuries in premature neonate twins. *Burns* 2005;31:76–84.
- Karlsen KA. The STABLE Program: Post-resuscitation/Pre-transport stabilization care of sick infants. 6th ed. Salt Lake City: STABLE, Inc; 2013.
- Sajben SE, Gibbs NF, Fallon-Friedlander S. Transillumination blisters in a neonate. *J Am Acad Dermatol* 1999;41:264–5.
- Keroack MA, Kotilainen HR, Griffin BE. A cluster of atypical skin lesions in well-baby nurseries and a neonatal intensive care unit. *J Perinatol* 1996;16:370–3.
- Hogeling M, Meddles K, Berk DR, et al. Extensive subcutaneous fat necrosis of the newborn associated with therapeutic hypothermia. *Pediatr Dermatol* 2012;29(1):59–63.
- Oza V, Treat J, Cook N, et al. Subcutaneous fat necrosis as a complication of whole-body cooling for birth asphyxia. *Arch Dermatol* 2010;146(8):882–5.
- Mahe E, De Prost Y. Subcutaneous fat necrosis of the newborn. *Ann Dermatol Venereol* 2007;134(5 Pt 1):494–9.
- Hicks MJ, Levy ML, Alexander J, et al. Subcutaneous fat necrosis of the newborn and hypercalcemia: Case report and review of the literature. *Pediatr Dermatol* 1993;10:271–6.
- Gu LL, Daneman A, Binet A, et al. Nephrocalcinosis and nephrolithiasis due to subcutaneous fat necrosis with hypercalcemia in two full-term asphyxiated neonates: sonographic findings. *Pediatr Radiol* 1995;25:142–4.
- Cutting KF. Impact of adhesive surgical tape and wound dressings on the skin, with reference to skin stripping. *J Wound Care* 2008; 17(4):157–8, 160–2.
- Lund CH, Nonato LB, Kuller JM, et al. Disruption of barrier function in neonatal skin associated with adhesive removal. *J Pediatr* 1997; 131(3):367–72.
- National Pressure Ulcer Advisory Panel (NPUAP). Pressure ulcer definition and stages. February; 2007. Available at: <http://www.npuap.org/resources/educational-and-clinical-resources/npuap-pressure-ulcer-stages-categories/> (Accessed February 2014).
- National Pressure Ulcer Advisory Panel (NPUAP). Pressure ulcer category/staging illustrations. Available at: <http://www.npuap.org/resources/educational-and-clinical-resources/pressure-ulcer-categorystaging-illustrations/> (Accessed February 2014).
- Curley MA, Quigley SM, Lin M. Pressure ulcers in pediatric intensive care: incidence and associated factors. *Pediatr Crit Care Med* 2003; 4(3):284–90.
- Schindler CA, Mikhailov TA, Kuhn EM, et al. Protecting fragile skin: nursing interventions to decrease development of pressure ulcers in pediatric intensive care. *Am J Crit Care* 2011; 20(1):26–35.
- Razmus I, Lewis L, Wilson D. Pressure ulcer development in infants: state of the science. *J Healthc Qual* 2008;30(5):36–42.
- Gershan LA, Esterly NB. Scarring alopecia in neonates as a consequence of hypoxemia–hypoperfusion. *Arch Dis Child* 1993;68: 591–3.
- Fischer C, Bertelle V, Hohlfeld J, et al. Nasal trauma due to continuous positive airway pressure in neonates. *Arch Dis Child Fetal Neonatal Ed* 2010;95(6):F447–51.
- Hogeling M, Fardin SR, Frieden IJ, et al. Forehead pressure necrosis in neonates following

- continuous positive airway pressure. *Pediatr Dermatol* 2012;29(1):45–8.
60. Curley MA, Razmus IS, Roberts KE, et al. Predicting pressure ulcer risk in pediatric patients: the Braden Q Scale. *Nurs Res* 2003;52(1):22–33.
 61. Baharestani MM, Ratliff CR. Pressure ulcers in neonates and children: an NPUAP white paper. *Adv Skin Wound Care* 2007;20(4):208–20.
 62. Cutler VE, Stretcher GS. Cutaneous complications of central umbilical artery catheterization. *Arch Dermatol* 1977;113:61–3.
 63. deSanctis N, Cardillo G, Rega AN. Gluteoperineal gangrene and sciatic nerve palsy after umbilical vessel injection. *Clin Orthop Rel Res* 1995;316:180–4.
 64. Letts M, Blasterah B, Al-Azzam S. Neonatal gangrene of the extremities. *J Pediatr Orthop* 1997;17:397–401.
 65. Cartwright GW, Schreiner RL. Major complication secondary to percutaneous radial artery catheterization in the neonate. *Pediatrics* 1980;65:139–41.
 66. Rudolph N, Wang HH, Dragutsky D. Gangrene of the buttock: A complication of umbilical artery catheterization. *Pediatrics* 1974;53:106–9.
 67. Serrano G, Aliaga A, Febrer I, et al. Perinatal gangrene of the buttock: A spontaneous condition. *Arch Dermatol* 1985;121:23–4.
 68. Bonifazi E, Meneghini C. Perinatal gangrene of the buttock: An iatrogenic or spontaneous condition? *J Am Acad Dermatol* 1980;3:596–8.
 69. Stokowski LA. Fundamentals of phototherapy for neonatal jaundice. *Adv Neonatal Care* 2011;11(Suppl. 5):S10–21.
 70. Kearns GL, Williams BJ, Timmons OT. Fluorescein phototoxicity in a premature infant. *J Pediatr* 1985;107:796–8.
 71. Burry JN, Lawrence JR. Phototoxic blisters from high furosemide dosage. *Br J Dermatol* 1976;94:495–9.
 72. Porat R, Gilbert S, Magilner D. Methylene blue-induced photosensitivity: an unrecognized complication. *Pediatrics* 1996;97:717–21.
 73. Mallon E, Wojnarowska F, Hope P, et al. Neonatal bullous eruption as a result of transient porphyria in a premature infant with hemolytic disease of the newborn. *J Am Acad Dermatol* 1995;33:333–6.
 74. Crawford RI, Lawlor ER, Wadsworth LD, et al. Transient erythropoietin of infancy. *J Am Acad Dermatol* 1996;35:833–4.
 75. Paller AS, Eramo LR, Farrell EE, et al. Purpuric phototherapy-induced eruption in transfused neonates: Relation to transient porphyria. *Pediatrics* 1997;100:360–4.
 76. McDonagh AF. Bilirubin, copper-porphyrins, and the bronze-baby syndrome. *J Pediatr* 2011;158(1):160–4.
 77. Ashley JR, Littler CM, Burgdorf WC, et al. Bronze baby syndrome. *J Am Acad Dermatol* 1985;12:325–8.
 78. Onishi S, Itoh S, Isobe K, et al. Mechanism of development of bronze baby syndrome in neonates treated with phototherapy. *Pediatrics* 1982;69:273–6.
 79. Purcell SM, Wians FH Jr, Ackerman NB Jr, et al. Hyperbilirubinemia in the bronze baby syndrome. *J Am Acad Dermatol* 1987;16:172–7.
 80. Ramamurthy RS, Harris V, Pildes RS. Subcutaneous calcium deposition in the neonate associated with intravenous administration of calcium gluconate. *Pediatrics* 1975;55:802–6.
 81. Sahn EE, Smith DJ. Annular dystrophic calcinosis cutis in an infant. *J Am Acad Dermatol* 1992;26:1015–17.
 82. Weiss Y, Ackerman C, Shmilovitz L. Localized necrosis of scalp in neonates due to calcium gluconate infusions: A cautionary note. *Pediatrics* 1975;56:1084–6.
 83. Puig L, Rocamora V, Romani J, et al. Calcinosis cutis following calcium chloride electrode paste application for auditory-brainstem evoked potentials recording. *Pediatr Dermatol* 1998;15:27–30.
 84. Hironaga M, Fujigaki T, Tanaka S. Calcinosis cutis in a neonate following extravasation of calcium gluconate. *J Am Acad Dermatol* 1982;6:392–5.
 85. Ahn SK, Kim KT, Lee SH, et al. The efficacy of treatment with triamcinolone acetonide in calcinosis cutis following extravasation of calcium gluconate: a preliminary study. *Pediatr Dermatol* 1997;14:103–9.
 86. Sell EJ, Hansen RC, Struck-Pierce S. Calcified nodules on the heel: A complication of neonatal intensive care. *J Pediatr* 1980;96:473–5.
 87. Rho NK, Youn SJ, Park HS, et al. Calcified nodules on the heel of a child following a single heel stick in the neonatal period. *Clin Exp Dermatol* 2003;28:502–3.
 88. Doelman D, Hadaway L, Bowe-Geddes LA, et al. Infiltration and extravasation: update on prevention and management. *J Infus Nurs* 2009;32(4):203–11.
 89. Wilkins CE, Emmerson AJ. Extravasation injuries on regional neonatal units. *Arch Dis Child Fetal Neonatal Ed* 2004;89: F274–5.
 90. Ramasethu, J. Prevention and management of extravasation injuries in neonates. *NeoReviews* 2004;5:e491–7.
 91. Thigpen JL. Peripheral intravenous extravasation: nursing procedure for initial treatment. *Neonatal Netw* 2007;26(6):379–84.
 92. Pettit J. Assessment of the infant with a peripheral intravenous device. *Adv Neonatal Care* 2003;3(5):230–40.
 93. Gorski LA, Hallock D, Kuehn SC, et al. Recommendations for frequency of assessment of the short peripheral catheter site. *J Infus Nurs* 2012;35(5):290–2.
 94. Alexander M, Corrigan A, Gorski L, et al. Infusion nursing an evidence based approach. 3rd ed. St Louis: Saunders Elsevier; 2010.
 95. Peabody JL, Emery JR. Noninvasive monitoring of blood gases in the newborn. *Clin Perinatol* 1985;12:147–60.
 96. Prizant TL, Lucky AW, Frieden IJ, et al. Spontaneous atrophic patches in extremely premature infants. *Arch Dermatol* 1996;132:671–4.
 97. Todd DJ. Anetoderma of prematurity. *Arch Dermatol* 1997;133:789.
 98. Miyasaka K, Ohata J. Burn, erosion, and 'sun'tan' with the use of pulse oximetry in infants. *Anesthesiology* 1987;67:1008–9.
 99. Evans NJ, Rutter N. Reduction of skin damage from transcutaneous oxygen electrodes using a spray on dressing. *Arch Dis Child* 1986;61:881–4.
 100. Golden SM. Skin craters – a complication of transcutaneous oxygen monitoring. *Pediatrics* 1981;67:514–16.
 101. Tobias JD. Transcutaneous carbon dioxide monitoring in infants and children. *Paediatr Anaesth* 2009;19(5):434–44.
 102. Mackenzie AR. Meatal ulceration following neonatal circumcision. *Obstet Gynecol* 1966;28:221–3.
 103. Frieden IJ, Chang MW, Lee I. Suture ligation of supernumerary digits and 'tags': an outmoded practice? *Arch Pediatr Adolesc Med* 1995;149:1284.
 104. Leber GE, Gosain AK. Surgical excision of pedunculated supernumerary digits prevents traumatic amputation neuromas. *Pediatr Dermatol* 2003;20:108–12.
 105. Kaddu S, Smolle J, Komericki P, et al. Auriculotemporal (Frey) syndrome in late childhood: an unusual variant presenting as gustatory flushing mimicking food allergy. *Pediatr Dermatol* 2000;17(2):126–8.
 106. Dizon MV, Fischer G, Jopp-McKay A, et al. Localized facial flushing in infancy. Auriculotemporal nerve (Frey) syndrome. *Arch Dermatol* 1997;133(9):1143–5.
 107. Sethuraman G, Mancini AJ. Familial auriculotemporal nerve (Frey) syndrome. *Pediatr Dermatol* 2009;26(3):302–5.
 108. Yokoyama T, Toga A, Hashida Y, et al. Hemifacial flushing after bathing and crying. *J Pediatr* 2012;160(6):1058–9.
 109. Smith SJ, Diehl N, Leavitt JA, et al. Incidence of pediatric Horner syndrome and the risk of neuroblastoma: a population-based study. *Arch Ophthalmol* 2010;128(3):324–9.
 110. George ND, Gonzalez G, Hoyt CS. Does Horner's syndrome in infancy require investigation? *Br J Ophthalmol* 1998;82(1):51–4.
 111. Meggitt SJ, Harper J, Lacour M, et al. Raised limb bands developing in infancy. *Br J Dermatol* 2002;147(2):359–63.
 112. Dyer JA, Chamlin S. Acquired raised bands of infancy: association with amniotic bands. *Pediatr Dermatol* 2005;22(4):346–9.
 113. Lateo SA, Taylor AE, Meggitt SJ. Raised limb bands developing in infancy. *Br J Dermatol* 2006;154(4):791–2.
 114. Russi DC, Irvine AD, Paller AS. Raised limb bands developing in infancy. *Br J Dermatol* 2003;149(2):436–7.
 115. Ford LS, Rogers M, Kemp AS, et al. Persistent linear bands in infancy acquired after local pressure: a consequence of mast cell activation? *Pediatr Dermatol* 2007;24(4):391–3.
 116. Beute TC. The use of a topical antihistamine in the treatment of raised linear bands of infancy. *Pediatr Dermatol* 2010;27(3):312–14.
 117. Mahajan D, Campbell-Lloyd S, Cook J, et al. NSW annual report describing adverse events following immunisation, 2010. *N S W Public Health Bull* 2011;22(9–10):196–208.
 118. Quinn P, Gold M, Royle J, et al. Recurrence of extensive injection site reactions following DTPa or dTpa vaccine in children 4–6 years old. *Vaccine* 2011;29(25):4230–7.
 119. Kemmeren JM, Vermeer-de Bondt PE, van der Maas NA. Discolored leg syndrome after vaccination – descriptive epidemiology. *Eur J Pediatr* 2009;168(1):43–50.
 120. Kienast AK, Mentze D, Hoeger PH. Nicolau's syndrome induced by intramuscular vaccinations in children: report of seven patients and review of the literature. *Clin Exp Dermatol* 2008;33(5):555–8.
 121. Nagore E, Torrelo A, Gonzalez-Mediero I, et al. Livedoid skin necrosis (Nicolau syndrome) due to triple vaccine (DTP) injection. *Br J Dermatol* 1997;137(6):1030–1.
 122. Erkek E, Tuncel F, Sanli C, et al. Nicolau's syndrome in a newborn caused by triple

- DTP (diphtheria-tetanus-pertussis) vaccination. *J Am Acad Dermatol* 2006;54(Suppl. 5): S241–2.
123. Sardana K, Garg VK, Bhushan P, et al. DPT vaccine-induced lipoatrophy: an observational study. *Int J Dermatol* 2007;46(10):1050–4.
124. Swerdlin A, Berkowitz C, Craft N. Cutaneous signs of child abuse. *J Am Acad Dermatol* 2007;57(3):371–92.
125. Pau-Charles I, Darwich-Soliva E, Grimalt R. [Skin signs in child abuse]. *Acta Dermosifiliogr* 2012;103(2):94–9.
126. Kos L, Shwayder T. Cutaneous manifestations of child abuse. *Pediatr Dermatol* 2006;23(4): 311–20.
127. Purdue GE, Hunt JL, Prescott PR. Child abuse by burning – an index of suspicion. *J Trauma* 1988;28(2):221–4.
128. Showers J, Garrison KM. Burn abuse: a four-year study. *J Trauma* 1988;28(11):1581–3.
129. Stratman E, Melski J. Scald abuse. *Arch Dermatol* 2002;138(3):318–20.
130. Carpenter RF. The prevalence and distribution of bruising in babies. *Arch Dis Child* 1999; 80(4):363–6.

Developmental Abnormalities

BETH ANN DROLET

Introduction

Developmental abnormalities of the skin are a diverse group of anomalies representing errors in morphogenesis. By definition, they are present at birth, although some are not evident in the neonatal period, but most present during infancy. They vary in severity from the inconsequential to the serious and, in some instances, represent a marker for significant extracutaneous anomalies.

Supernumerary mammary tissue

Accessory mammary tissue (supernumerary nipples, accessory nipple, polythelia, polymastia) may consist of true glandular tissue (accessory breasts), areola, nipples, or a combination thereof. It is often bilateral and found along the course of the embryologic breast lines, which run from the axilla to the inner thigh. Accessory nipples are the most common variant, occurring in as many as 2% of females, manifesting clinically as soft, brown, pedunculated papules (Fig. 9.1). In the newborn, the lesions are often very subtle, appearing as a light brown or pearly 1–3 mm macule. Familial occurrence has been reported.

Extracutaneous findings

It has been suggested that renal and urogenital malformations occur with increased frequency in infants with polythelia, although the results of published studies are conflicting, with incidence figures ranging from zero to approximately 10%.^{1–6}

Diagnosis

The diagnosis is usually made clinically but may be confirmed by histologic demonstration of mammary tissue. An accessory nipple will show epidermal thickening, pilosebaceous structures, and smooth muscle, with or without true mammary glands.⁷ The differential diagnosis includes melanocytic nevus, neurofibroma, verruca, or skin tag.

Treatment

Complete surgical excision is usually recommended if there is glandular tissue because enlargement at puberty may cause pain and embarrassment. Small accessory nipples need not be excised. Breast carcinoma has also been reported in ectopic mammary tissue in an adult.⁸

Preauricular pits and sinuses

The auricle is formed by fusion of six tubercles derived from the first and second branchial arches. Incomplete fusion may lead to entrapment of epithelium, forming cysts that communicate to the skin surface through sinuses.⁹ If the cyst and sinus

are obliterated, a pit is left behind. Preauricular pits are common and may be inherited in an autosomal dominant fashion. They manifest as small depressions at the anterior margin of the ascending limb of the helix (Fig. 9.2).

Preauricular cysts present as tender swellings in the preauricular region; occasionally they are bilateral. If there is a sinus tract, fluid or pus may drain from a small opening just anterior to the ascending portion of the helix (Fig. 9.3). Most patients with preauricular cysts will have a history of recurrent infections.

Extracutaneous findings

The purported association of preauricular pits, accessory tragi, and sinuses with renal abnormalities is controversial.¹⁰ The most recent recommendations reserve renal ultrasound screening for patients with additional dysmorphic features, a family history of deafness, auricular and/or renal malformations, or a maternal history of gestational diabetes.¹¹ Patients with preauricular pits or tags may have a higher incidence of hearing impairment, although studies regarding this are conflicting. Most studies do suggest screening for hearing deficits if the universal newborn hearing screen is not routinely performed.¹²

Diagnosis and treatment

The diagnosis is usually clinically apparent. The sinuses and cysts are lined by stratified squamous epithelium. Surgical excision of preauricular cysts and sinuses is indicated to prevent secondary infection. An experienced surgeon should perform the excision because the procedure may be complicated by multiple cysts along a tract that ends at the periosteum of the auditory canal.

Accessory tragi

The tragus is derived from the dorsal portion of the first branchial arch. Accessory tragi (erroneously referred to as preauricular ‘tags’) are always congenital and manifest as pedunculated, flesh-colored, soft, round papules usually arising on or near the tragus. They may occur anywhere from the preauricular region to the corner of the mouth, following the line of fusion of the mandibular and maxillary branches of the first branchial arch (Fig. 9.4). They may be bilateral and/or multiple. The same hearing and renal screening recommendations discussed above regarding preauricular pits should be followed. Accessory tragi are usually isolated defects, but may be associated with other developmental abnormalities of the first branchial arch.¹³ Goldenhar syndrome (oculoauriculovertebral syndrome) manifests as epibulbar dermoids, vertebral anomalies, and accessory tragi (Box 9.1).¹⁴



Figure 9.1 Accessory nipple.

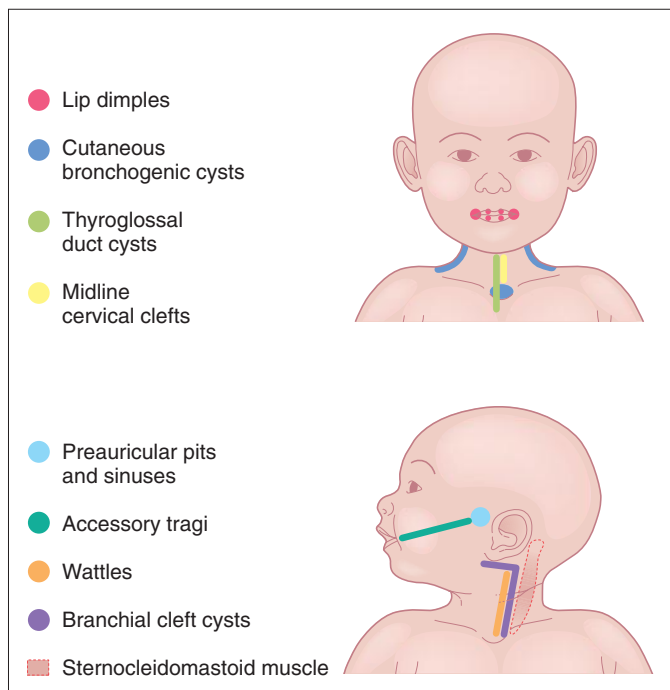


Figure 9.2 Common locations of congenital cysts, clefts, and sinuses.



Figure 9.3 Preauricular sinus with superinfection.

BOX 9.1 GENETIC DISORDERS ASSOCIATED WITH PREAURICULAR ANOMALIES

PREAURICULAR PITS/SINUSES

- Branchio-oto-renal syndrome
- Goldenhar syndrome
- Cat eye syndrome

ACCESSORY TRAGI

- Goldenhar syndrome
- Treacher–Collins syndrome
- Townes–Brook syndrome
- VACTERL
- Wolf–Hirschhorn syndrome (4p deletion syndrome)
- Delleman syndrome

Diagnosis and treatment

The diagnosis is usually clinically apparent. Histologically, there are numerous tiny hair follicles with prominent connective tissue. A central core of cartilage is usually present.¹⁵ Accessory tragi should be removed by careful surgical dissection because most contain cartilage that may extend deeply, contiguous with the external ear canal. They are *not* skin tags and should not be tied off with suture material.¹⁶

Cervical tabs/wattles/congenital cartilaginous rests of the neck

Cervical tabs are soft, pedunculated, irregular nodules occurring on the neck along the anterior border of the sternocleidomastoid muscle. They are thought to be remnants of branchial arches and tend to occur along branchial arch fusion lines (Fig. 9.5). Histologically, they show lobules of mature cartilage embedded in collagen. The lesions do not extend deeply, but complete surgical excision is the treatment of choice because ligation may result in complications.^{17,18}

Supernumerary digits (rudimentary polydactyly)

Supernumerary digits arise from the lateral surface of a normal digit. They are most common on the ulnar surface of the fifth digit, but may occur on any finger. They are congenital and may be bilateral or multiple. Some are small pedunculated papules, whereas others are normal-sized digits containing both cartilage and nail (Fig. 9.6). These lesions should be surgically excised and the associated nerve dissected if present. Ligating the supernumerary digit with suture material without completely removing the nerve may result in skin necrosis, infection, and painful neuromas in adult life.¹⁶

Branchial cysts, branchial clefts, and branchial sinuses

Branchial cysts are congenital malformations; however, they are not often apparent clinically until the first or second decade of life. They are painless, mobile, cystic swellings in the neck that may swell during respiratory tract infections. Most measure 1–2 cm, although they may be as large as 10 cm. Branchial cysts derived from the second branchial arch are the most common and are found on the lateral aspect of the upper neck, along the sternocleidomastoid muscle (Fig. 9.7).



Figure 9.4 (A,B) Accessory tragi in the preauricular region. (C) Accessory tragus in the preauricular region and in the much less common region of the lateral commissure of the mouth.



Figure 9.5 Cartilaginous rest of the neck.

Branchial cleft cysts derived from the first branchial arch are very rare and are located in the periauricular area or on the upper neck anterior to the sternocleidomastoid muscle. Definitive diagnosis is made by histologic examination of the lesions. Branchial cysts are lined by stratified squamous epithelium or, rarely, by ciliated columnar epithelium. Additionally, there is often abundant lymphoid tissue. Squamous cell carcinomas arising in these cystic lesions have been described in adults.¹⁹

Branchial sinuses and branchial clefts are thought to be remnants of the branchial cleft depressions. They are usually present at birth or noted during the first few years of life. The most common location is along the lateral lower third of the neck. Often a skin tag with a small amount of cartilage is associated with the pit. Branchial cleft anomalies should be surgically excised to prevent infection, with careful attention to the possibility of a true fistula connecting to the tonsillar oropharynx. Preoperative imaging may be necessary to exclude the possibility of true fistulae.

Thyroglossal duct cysts

Thyroglossal duct cysts are the most common cause of a congenital neck mass. They result from the persistence of a tract formed during the migration of the rudimentary thyroid gland from the base of the tongue to the anterior cervical regions. The most common location is on, or just lateral to, the midline neck in the area of the hyoid bone, but they may be found anywhere from the posterior tongue to the suprasternal notch. Most thyroglossal duct cysts present in childhood as an asymptomatic neck mass that moves upward with tongue protrusion or swallowing. Occasionally, ectopic thyroid tissue can be found in these cysts, and an association with thyroid cancer has been reported. The treatment is complete surgical excision in order to prevent growth and infection. Preoperative imaging with high-resolution ultrasound is important to confirm the diagnosis and identify the presence of a normal thyroid gland.²⁰

Cutaneous bronchogenic cysts and sinuses

Bronchogenic cysts are usually found within the chest or mediastinum but may also occasionally be found in the skin. The most

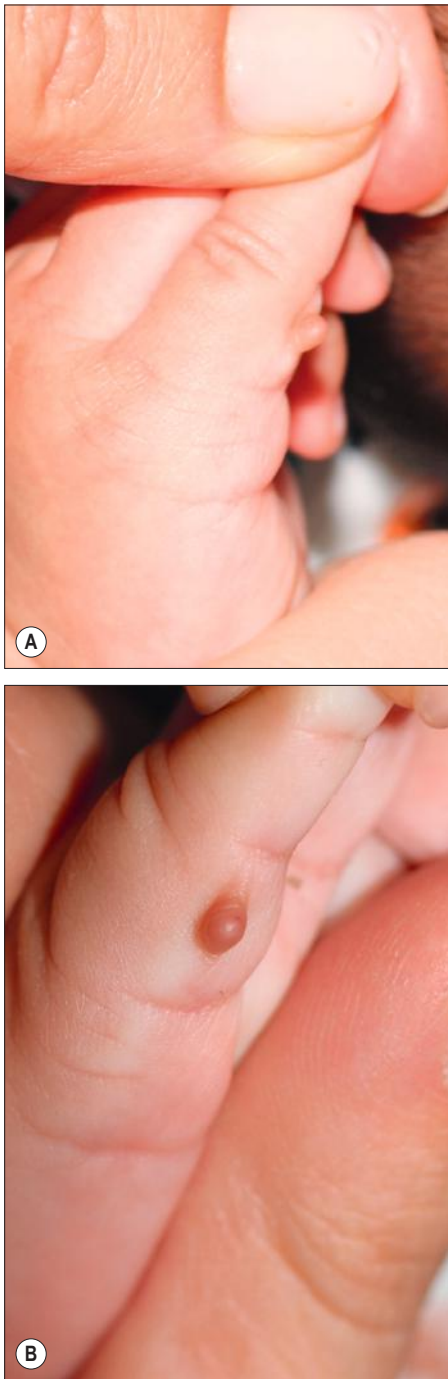


Figure 9.6 (A,B) Supernumerary digits.

common cutaneous location is in the subcutaneous tissue at the suprasternal notch, but other locations include the lateral neck, scapula, and presternal area. Thus, these cysts should be included in the differential diagnosis of both lateral and midline neck masses. The cysts are congenital and usually apparent at birth. They are asymptomatic, small cystic swellings that will gradually enlarge over time and may discharge a mucoid material. These lesions are not usually associated with other malformations and do not connect to underlying structures.^{21,22} The diagnosis is made by histologic examination of the nodule or sinus. Bronchogenic cysts are lined by lamina propria and a pseudostratified columnar ciliated epithelium with goblet cells.²³



Figure 9.7 Branchial cyst on the lateral region of the neck.



Figure 9.8 Multiple inclusion cysts along the ventral surface of the penis.

The cyst wall may contain smooth muscle, mucus glands, and cartilage and lymphatic tissue may or may not be present.

The differential diagnosis includes branchial arch cysts, thyroglossal duct cysts, teratomas, and heterotopic salivary gland tissue. The treatment is complete surgical excision to prevent infection.

Median raphe cysts

Median raphe cysts (congenital sinus and cysts of the genitoperineal raphe, mucous cysts of the penile skin, parametateal cysts) are the consequence of incomplete fusion of the ventral aspect of the urethral or genital folds. The cysts can occur at any site on the ventral surface of the male genital region, including the parametateum, glans penis, penile shaft, scrotum, or perineum. In most cases they remain asymptomatic and do not interfere with urinary or sexual function. Rarely they can enlarge or become superinfected. In infancy they manifest as small, soft, flesh-colored papules along the ventral aspect of the penis in the line of the median raphe, however, they may enlarge during adolescence (Fig. 9.8). The cysts are lined with



Figure 9.9 Supraumbilical raphe in an infant with PHACE syndrome.

pseudostratified columnar epithelium, except at the distal penis, where they have stratified epithelium.²⁴

Ventral midline clefts/defects

SUPRAUMBILICAL CLEFT

Disruption of abdominal wall fusion causes midline defects of variable degree, often involving the heart and sternum, as well as the abdominal wall. Supraumbilical raphes are linear, midline clefts that occur superior to the umbilicus (Fig. 9.9). A well-described association of supraumbilical raphe and/or sternal clefting has been described in association with hemangiomas and PHACE syndrome (see Chapter 21).^{25–27}

MIDLINE CERVICAL CLEFTS

This rare abnormality of the midline ventral neck presents as a small skin tag superiorly with a linear, vertically oriented atrophic patch. At the inferior aspect of the patch there is often a small sinus containing ectopic salivary tissue.²⁸ Midline cervical clefts can be associated with cleft lip, palate, mandible, chin, tongue, or midline neck hypoplasia.²⁹ Excision with serial Z-plasties is the treatment of choice.

Cutaneous signs of neural tube dysraphism

The skin and the nervous system share a common ectodermal origin. Separation of the neural and cutaneous ectoderm occurs early in gestation, at the same time the neural tube is fusing. This shared embryologic origin explains the simultaneous occurrence of congenital malformations of the skin and neural tube dysraphism, which is an incomplete closure or defective fusion. Open neural tube defects are often large and diagnosed in utero or at birth; however, closed or occult neural tube defects often present solely with congenital abnormalities of the skin overlying the defect. It is important to recognize these cutaneous markers and screen with the appropriate radiologic imaging techniques. A general knowledge of embryology and formation and closure of the neural tube is useful in identifying which cutaneous markers are highly indicative of underlying defects. The neural tube is no longer believed to fuse in a zipper-like



Figure 9.10 Cutaneous 'hotspots' for neural tube dysraphism are depicted by the circles. The arrows represent the direction of fusion of each neural tube segment.

fashion, but rather in a segmental, noncontiguous pattern.³⁰ This theory is supported by the clinical observation of cutaneous 'hotspots' for dysraphic conditions. Each hotspot corresponds to a fusion point of the various segments of the neural tube (Fig. 9.10).

CRANIAL DYSPHISM

Cephaloceles/cutaneous neural heterotopias

The term *cutaneous neural heterotopia* was introduced to describe ectopic leptomeningeal or glial tissue found in the subcutaneous tissue or dermis of the skin. These malformations are the result of incomplete or faulty closure of the neural tube. Cephalocele is the general term for congenital herniation of intracranial structures through a cranial defect. Encephalocele is herniation of both glial and meningeal tissue. Meningocele is cephalocele in which only the meninges and cerebrospinal fluid herniate through a calvarial defect. Large encephaloceles and meningoceles pose no diagnostic problem and are usually easily diagnosed prenatally or at birth. Smaller or atretic encephaloceles and meningoceles may be mistaken for cutaneous lesions such as hematomas, hemangiomas, aplasia cutis, dermoid cysts, or inclusion cysts. Several terms have been used to describe these smaller lesions (Box 9.2). These various classifications were derived from the amount and type of neural tissue present, as well as the degree of connection to the central nervous system. Unfortunately, it is not possible to predict the degree of CNS connection on clinical grounds alone. Therefore, all congenital exophytic scalp nodules should be evaluated thoroughly, as 20–37% of congenital, nontraumatic scalp nodules connect to the underlying central nervous system.^{31,32}

Cutaneous findings

Cephaloceles occur in the frontal, parietal, and occipital regions. They are usually midline, although they may also be found

BOX 9.2 TERMS USED TO DESCRIBE CUTANEOUS NEURAL HETEROTOPIAS

- Heterotopic meningeal nodules
- Ectopic brain tissue
- Heterotopic brain tissue/nodules
- Meningioma
- Rudimentary encephalocele/meningocele
- Atretic encephalocele/meningocele
- Vestigial encephalocele/meningocele

1–3 cm lateral to the midline. Small cephaloceles are clinically heterogeneous; their appearance dictated by the type and amount of cutaneous ectoderm overlying the lesion. They may be covered with normal skin, or have a blue, translucent, or glistening surface. There is usually a disruption of the surrounding and overlying normal hair pattern. They are soft, compressible, round nodules that increase in size when the baby cries or with a Valsalva maneuver.

The association of a congenital scalp mass with other cutaneous abnormalities makes the diagnosis of cranial dysraphism highly suspicious. Stigmata include hypertrichosis, or the ‘hair-collar sign,’ capillary malformations, and cutaneous dimples and sinuses.^{33,34} The hypertrichosis may overlie the nodule, surround a small sinus, or encircle the nodule (hair-collar sign). A hair collar is defined as a congenital ring of hair that is usually denser, darker, and coarser than the normal scalp hair. When found encircling an exophytic scalp nodule, it is highly suggestive of cranial dysraphism (Figs 9.11, 9.12).^{33,34} The hair-collar sign may be found in association with encephaloceles, meningoceles, atretic encephaloceles, atretic meningoceles, and heterotopic brain tissue. A hair collar may also be seen with some lesions of aplasia cutis; thus this sign is not entirely specific.³⁵ Cranial neural tube defects may also be associated with overlying red, blanchable patches that represent capillary malformations. The combination of a hair-collar sign and capillary malformation surrounding a congenital scalp lesion is almost always indicative of a dysraphic condition (Fig. 9.11).³⁴

Extracutaneous findings and diagnosis

From a clinical standpoint, encephaloceles, meningoceles, atretic cephaloceles, and heterotopic brain tissue are virtually impossible to differentiate. All congenital midline scalp nodules carry a significant risk of intracranial connection and should have radiologic imaging studies performed before surgical removal to prevent complications such as meningitis. Membranous aplasia cutis congenita (ACC) has many overlapping clinical features (including the hair-collar sign); in addition, the loose fibroconnective tissue seen histologically is very similar to the changes observed surrounding encephaloceles.³³ The presence of a palpable nodule within a lesion of ACC, however, is uncommon and should always prompt further evaluation. Magnetic resonance imaging (MRI) is the most sensitive method for detecting small cephaloceles with intracranial connections.

Differential diagnosis and management

Included in the differential diagnoses of congenital scalp nodules are pilomatrixoma, epidermoid cyst, lipoma, osteoma, eosinophilic granuloma, hemangioma, sinus pericranii, dermoid cyst, leptomeningeal cyst, and cephalohematoma.³⁶ Surgical correction is indicated for all cephaloceles.



Figure 9.11 Dense ‘hair collar’ surrounding a vesicular scalp nodule found to be a meningocele.



Figure 9.12 Congenital midline nodule with hair collar and capillary malformation. MRI confirmed an atretic encephalocele.

NASAL GLIOMAS

Gliomas are rests of ectopic neural tissue and differ from frontal encephaloceles in that they do not have a patent intracranial communication. The lesions may be external, intranasal, or combined. Clinically, they are firm, noncompressible, non-tender skin-colored to red-purple nodules at the root of the nose. Gliomas may be covered with nasal mucosa or normal skin; they are often associated with telangiectasia and misdiagnosed as hemangiomas. They may widen the nasal bone, giving the appearance of hypertelorism. They are congenital and do not proliferate. Additionally, they do not respond to oral steroids or propranolol, which helps to differentiate them from hemangiomas. Immediate neurosurgical referral is required for surgical removal and reconstruction.

CRANIAL DERMOID CYSTS AND SINUSES

Dermoid cysts are congenital subcutaneous lesions that are distributed along embryonic fusion lines. The cysts may occur within the fusion lines of the facial processes or along the neural axis. They represent faulty development and may include both epidermal and dermal elements.

Cutaneous findings

Although dermoid cysts are always congenital, they may not be noted until early childhood, when they begin to enlarge. They can occur anywhere on the face, scalp, or spinal axis but are most frequently seen overlying the anterior fontanelle, at the junction of the sagittal and coronal sutures on the scalp, on the upper lateral region of the forehead within or near the eyebrow, and in the submental region.^{31,37–40} They are firm, nontender, noncompressible, blue or skin-colored nodules measuring 1–4 cm (Figs 9.13, 9.14). They do not transilluminate or enlarge with a Valsalva maneuver. The overlying skin is normal, unless



Figure 9.13 Small midline nasal dermoid cyst.



Figure 9.14 (A) Lateral dermoid cyst. (B) Lateral brow dermoid cyst. (A: Courtesy of Dr Victoria Barrio.)

there is an external connection in the form of a pit or a sinus. Dermoid cysts often adhere to the underlying periosteum and may feel like abnormalities of the bone.

Dermal sinuses are 1–5 mm tracts that typically connect a dermoid cyst to the skin surface. They are midline and are found on the nose, occipital scalp (Fig. 9.15) and anywhere along the spinal axis. They may become clinically apparent when they become infected and drain purulent material. A small tuft of hair is often found protruding from the orifice. If the sinus and/or cyst communicates directly with the central nervous system, the patient is at risk for meningitis. The sinus serves as an occult portal of entry for bacteria, often causing recurrent meningitis that is culture-positive for skin flora. *Staphylococcus aureus* meningitis should be considered secondary to a dermal sinus until proved otherwise, and a thorough search for a cutaneous fistula should be carried out, which may necessitate shaving the scalp hair.⁴¹ All midline dermal sinuses should have radiologic imaging prior to surgical excision. Probing these lesions is contraindicated, given the potential risk of meningitis.

Extracutaneous findings

Midline or nasal dermoid cysts are of the greatest concern because 25% have an intracranial connection.³¹ Nasal dermoid cysts may occur anywhere from the glabella to the tip of the nose; a nasal pit or sinus is present in about half the cases.³⁷ The pit often leads caudally to a dermal sinus and eventuates in a cyst that may be either external or within the nasal bones. If the dermoid cyst connects to the central nervous system, cerebrospinal fluid may drain from the sinus. As with nasal gliomas, the patient may have the appearance of hypertelorism if the cyst has widened the nasal bones. Nasal dermoids should always be excised, because over time, they enlarge and damage the nasal bones. Dermoid cysts that are not midline should also be excised because they have the potential for infection. Dermoids of the lateral eyebrow area do not have central nervous system connections and may be surgically excised, either directly or using an endoscopic approach via a scalp incision to avoid facial scarring (Fig. 9.14). Lateral brow dermoids appear deceptively superficial, but most are actually located beneath muscle, so that either removal must be via an endoscopic approach or the surgeon must be prepared to dissect through the muscle to remove the cyst.

Diagnosis

Definitive diagnosis is made by histologic examination of the lesions. Dermoid cysts are usually found in the subcutaneous tissue and are lined by stratified squamous epithelium, often containing hair follicles, sebaceous glands, and sweat glands. The lumen may contain keratin, lipid, and hair. Radiologic imaging is a very sensitive screening method and should be undertaken prior to surgical intervention. Currently, the most sensitive study is MRI. Computed tomography (CT) may better delineate bony defects and may also be necessary for surgical planning, especially in the nasal region. Although plain radiographs were used extensively in the past, they are not sensitive and should not be used for screening.

Spinal dysraphism

Spinal dysraphism, or incomplete closure of the spinal axis, encompasses many congenital anomalies of the spine. Larger,

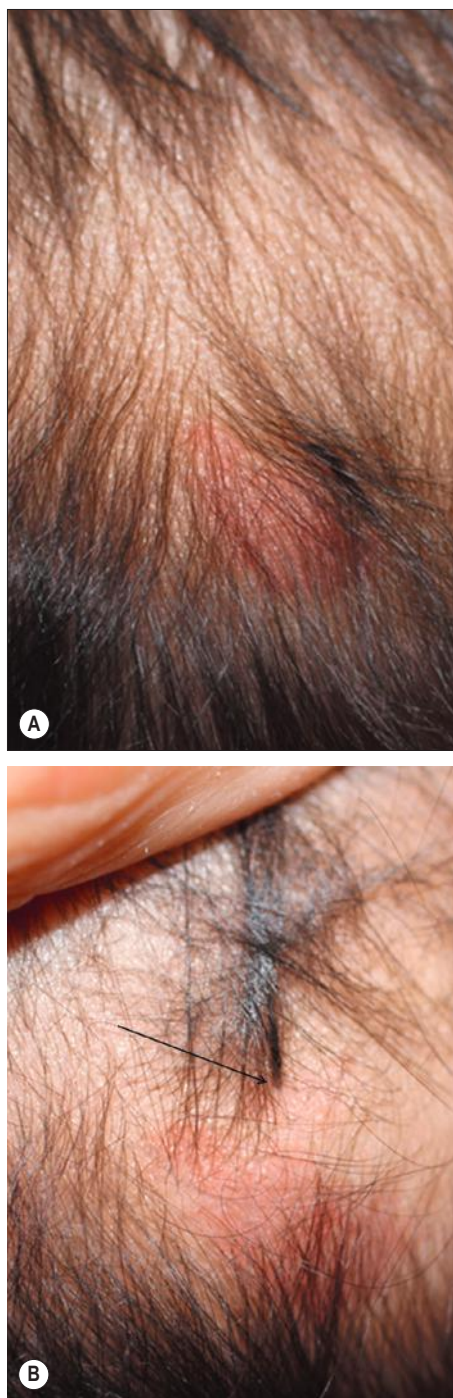


Figure 9.15 (A,B) Small atrophic plaque with tuft of hair located on the occipital scalp – MRI confirmed sinus tract.

open defects, such as meningocele, are usually obvious at birth and fall within the purview of the neurosurgeon. However, small or occult malformations covered with skin may have subtle signs and be asymptomatic. Early diagnosis is imperative, as it may prevent irreversible neurologic damage caused by tethering of the spinal cord. A diagnosis of occult spinal dysraphism is often suspected solely on the basis of overlying cutaneous findings, particularly in the newborn. Cutaneous markers are found in 50–90% of patients with spinal dysraphism.^{42–51}

BOX 9.3 CUTANEOUS LESIONS ASSOCIATED WITH SPINAL DYSRAPHISM

HIGH INDEX OF SUSPICION

- Presence of two or more cutaneous lesions
- Hypertrichosis
- Dimples (large, >2.5 cm from the anal verge, atypical)
- Acrochordons/pseudotails/true tails
- Lipomas
- Hemangiomas
- Aplasia cutis or scar
- Dermoid cyst or sinus

LOW INDEX OF SUSPICION

- Telangiectasia
- Capillary malformation (port-wine stain)
- Hyperpigmentation
- Melanocytic nevi
- Small sacral dimples, <2.5 cm from the anal verge
- Teratomas

Cutaneous findings

The cutaneous lesions that should alert the physician to an underlying occult spinal dysraphism are listed in Box 9.3. Most are found on or near the midline in the lumbosacral region; however, similar markers in the cervical or thoracic regions may also be indicative of an underlying malformation. The literature suggests that certain skin lesions are more indicative than others of underlying malformation.^{42–53} Tavafoghi and colleagues⁵¹ reviewed 200 cases of spinal dysraphism and found that 102 had cutaneous signs. Other studies have documented an even higher incidence of cutaneous malformations (71–100%). Unfortunately, no prospective studies have been carried out to determine what percentage of children with cutaneous anomalies overlying the spinal axis has occult dysraphism.

Congenital cutaneous anomalies of the lumbosacral region should be evaluated in the context of a full history and physical examination, particularly in the older child. The history should include questions about additional congenital malformations, family history of neural tube defects, weakness or pain in the lower extremities, abnormal gait, scoliosis, difficulties with toilet training or incontinence, recurrent urinary tract infections, and recurrent meningitis. The vertebrae should be palpated for any defects or abnormalities. Examination of the rectum and genitalia is also indicated, as there are often related congenital abnormalities of the urogenital system.^{54–56} The gluteal cleft should be examined carefully for small acrochordons or sinuses; it should be straight and the buttocks symmetric. If the gluteal cleft deviates, it is suggestive of an underlying mass such as a lipoma or meningocele. Examination of the lower extremities is important in older children because they may have trophic changes secondary to nerve damage.

HYPERTRICHOSIS

Localized lumbosacral hypertrichosis, or ‘hairy patch,’ is usually present at birth. The hair may be dark or light. The texture of the hair can vary but is frequently described as silky (faun tail nevus). The hypertrichosis is often V-shaped and poorly circumscribed. Prominent hypertrichosis is commonly associated with other cutaneous stigmata of spinal dysraphism and is

highly indicative of a spinal defect. However, hypertrichosis in the lumbosacral region can also be a normal finding, especially in certain ethnic or racial groups, and it may be difficult to decide whether or not further evaluation is indicated. Referral to a neurologist or neurosurgeon for a more complete neurologic examination may be a prudent measure in these cases.

LIPOMAS

Lipomas associated with spinal dysraphism are thought to be congenital and are also highly indicative of an underlying defect. Unlike acquired lipomas, they may be poorly circumscribed and feel more like an area of increased subcutaneous fat than a discrete lesion. They are frequently associated with a vascular stain or infantile hemangioma. The lipoma may lie in the dermis or the spinal canal, and often penetrates from the dermis through a vertebral defect into the intraspinal space (lipomyelomeningocele). Intraspinal lipomas are a common cause of tethered cord. Appropriate radiologic investigation of lumbosacral lipomas must be performed before surgical excision, and a neurosurgeon should be involved as small intraspinal connections may be missed, even with the most sensitive radiologic imaging.

HEMANGIOMAS, TELANGIECTASIAS, AND CAPILLARY MALFORMATIONS

Infantile hemangiomas are proliferative vascular tumors that may be present at birth or develop in the first months of life. In 1986, Goldberg and coworkers described five children with large sacral hemangiomas and several other associated abnormalities.⁵⁵ Three of the five had spinal dysraphism (lipomyelomeningocele). In 1989, Albright and colleagues⁴² reported seven infants with lumbar hemangiomas and a tethered spinal cord. Although several subsequent reports have supported this association, the true risk of spinal dysraphism with solitary infantile hemangiomas has been debated. Much of the controversy stems from imprecise terminology ('capillary hemangiomas') and the lumping of vascular stains with infantile hemangiomas. A recent prospective study helped to clarify the issue, demonstrating a 52% risk of spinal dysraphism with infantile hemangiomas >2.5 cm in the midline lumbosacral region.⁵⁷ Intraspinal lipomas were the most frequent association, but intraspinal hemangiomas were found in 45% of the cases. Hemangiomas associated with spinal dysraphism are usually large (>4 cm) and overlie the midline of the lumbar or sacral region (Figs 9.16, 9.17). There is often a small skin defect or ulceration⁵⁸ within the center of the hemangioma. The hemangiomas may be associated with other cutaneous stigmata, such as lipoma, acrochordon, or dermal sinus. In addition, hemangiomas may be observed in a constellation of congenital malformations seen in the caudal regressions syndromes. Although various acronyms have been coined to describe this constellation of abnormalities (PELVIS syndrome, SACRAL syndrome, and LUMBAR syndrome), they all represent the same clinical spectrum and manifest as lumbosacral hemangioma, anogenital abnormalities, and spinal dysraphism. These cases are difficult to manage because the hemangiomas can ulcerate, and surgical repair of the tethered cord often may have to be delayed until the hemangioma partially regresses.

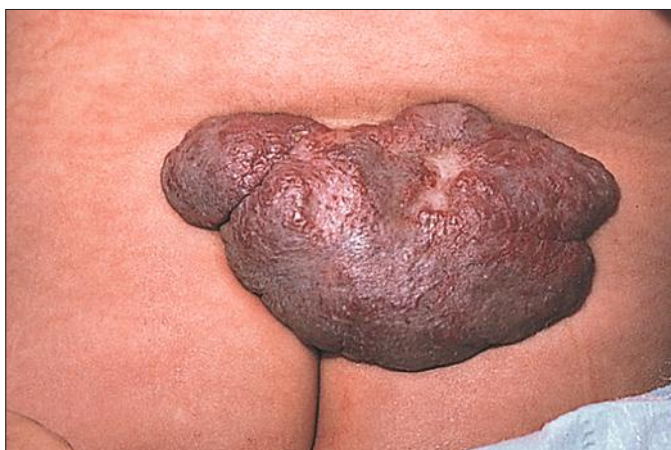


Figure 9.16 Midline sacral hemangioma in a patient with an occult lipomyelomeningocele.



Figure 9.17 Midline sacral superficial hemangioma in a patient with an underlying lipoma and tethered spinal cord.

Reports of telangiectatic patches are most likely describing nascent or partially regressed hemangiomas. Enjolras and colleagues⁵⁹ reported two patients with cervical spinal dysraphism with an overlying capillary malformation (port-wine stain), but spinal dysraphism associated with a midline, lumbosacral capillary malformation without additional clinical findings is probably uncommon. Two small studies have shown a low, although genuine, incidence of spinal dysraphism associated with a solitary capillary malformation of the lumbosacral region.^{60,61} Further investigation is needed to completely clarify the need for imaging in these infants. A neurologic consultation may be warranted.

DIMPLES, SINUSES, APLASIA CUTIS, AND CONGENITAL SCARS

Lumbosacral dimples are common, but can occasionally be a sign of spinal dysraphism.^{62,63} Most infants with coccygeal or lower sacral dimples falling within the gluteal crease, are normal.⁶⁴ Dimples that are deep, large (>0.5 cm), located in the



Figure 9.18 Deep sacral dimple above the gluteal crease.



Figure 9.19 Dimple on buttock with bluish discoloration suggestive of a lateral congenital spinal dermal sinus.

superior portion or above the gluteal crease (>2.5 cm from the anal verge), or associated with other cutaneous markers should be radiologically imaged (Fig. 9.18).⁶¹ Deep or draining dimples may actually be dermal sinuses, communicating directly with the spinal canal. They may also be located off the midline, on the buttock (Fig. 9.19).⁶⁵ These lesions should not be probed, but instead should prompt MRI studies and neurosurgical consultation.

Aplasia cutis has rarely been reported in the lumbosacral region and in that site may be associated with underlying spinal dysraphism (Fig. 9.20).⁴³ Scar-like defects have also been described in patients with spinal dysraphism, and may in fact be a variant of aplasia cutis.⁵⁵ The scar-like regions found in lumbosacral hemangiomas may represent a similar phenomenon.

ACROCHORDONS, TAILS, AND PSEUDOTAILS

Acrochordons are small skin-covered sessile or pedunculated papules or nodules (Fig. 9.21). Histologically they are composed of epidermis and a dermal stalk. A true human tail (persistent vestigial tail) is rare and is differentiated from a pseudotail and an acrochordon by the presence of a central core of mature fatty



Figure 9.20 Oval defect of aplasia cutis overlying the lumbosacral spine in an infant with spinal dysraphism.



Figure 9.21 Human tail with underlying lipoma in an infant with lipomyelomeningocele.

tissue, small blood vessels, bundles of muscle fibers, and nerve fibers. A pseudotail is a stump-like structure considered to be a hamartoma composed of fatty tissue and, often, cartilage. Clinically, these lesions are difficult to distinguish and all have been associated with spinal dysraphism.^{45,47,51,55,66} Preoperative radiologic investigation is indicated in all cases.

Diagnosis

A definitive diagnosis of spinal dysraphism is made only at surgery. Radiologic imaging provides a sensitive screening method. MRI remains the gold standard; high-resolution ultrasound is a noninvasive alternative in an infant of less than 3 months of age, but its sensitivity is low, making it an unreliable screening tool.^{67–73} It is often useful to speak to the radiologist before ordering the examination because the technology is changing rapidly and will vary by institution. Urodynamic studies are increasingly being used as another modality for assessing spinal cord function in settings where radiologic findings are equivocal.⁷⁴

Aplasia cutis

Aplasia cutis is a general term used to describe focal, congenital defects of the skin. The condition is rare and its true incidence is unknown. Although several theories have been proposed as to its pathogenesis, most authors believe that aplasia cutis has no single underlying cause but is rather a clinical finding, resulting from a variety of events that occur in utero. Several classifications of aplasia cutis have been proposed (Table 9.1).⁷⁵

When evaluating a newborn with aplasia cutis, particular attention should be given to the morphology and the distribution of the defects, because this may be helpful in determining the etiology, possible associated malformations, and prognosis (Table 9.2). For example, infants with large (>3 cm), angular defects of aplasia cutis on the bilateral extremities have generalized increased skin fragility, the result of a genetic deficiency, and almost all have been classified as having epidermolysis bullosa. This is a lifelong affliction and will have immediate

implications for the care of the infant. Large, irregular scalp defects may be seen with trisomy 13 (Fig. 9.22). Table 9.3 correlates the clinical findings with the proposed etiology and associations.

Cutaneous findings

Membranous aplasia cutis is the most common form of the condition. It occurs primarily on the scalp, but may also be seen on the lateral aspects of the face (focal facial dermal hypoplasia). The lesions are usually small (<1 cm), oval, or round and are well-circumscribed, with a 'punched-out' appearance (Fig. 9.23). At birth, the surface is atrophic, often thin, glistening, and membrane-like. Scar-like lesions in the same configuration are more common in older children. Rarely, the lesions may be bullous at birth, containing a thick, clear fluid (Fig. 9.24). The bullous lesions may drain spontaneously and reform, eventually flattening to the more typical appearance. Defects of membranous aplasia cutis are often multiple, occurring in a linear

TABLE 9.1 A classification of aplasia cutis congenita

Category	Body area affected	Associated abnormalities	Inheritance
Group 1: scalp ACC without multiple anomalies	Scalp, usually vertex	Cleft lip and palate; tracheoesophageal fistula; double cervix and uterus; patent ductus arteriosus; omphalocele; polycystic kidney; mental retardation; cutis marmorata telangiectatica congenita	Autosomal dominant or sporadic
Group 2: scalp ACC with associated limb abnormalities (most cases are Adams–Oliver syndrome)	Midline scalp	Limb reduction abnormalities; 2–3 syndactyly; clubfoot; nail absence or dystrophy; skin tags on toes; persistent cutis marmorata; encephalocele; woolly hair; hemangioma; heart disease; cryptorchidism; postaxial polydactyly (1 family)	Autosomal dominant
Group 3: Scalp ACC with associated epidermal and organoid nevi	Membranous scalp lesions, may be asymmetric, solitary or multiple	Cephaloceles; corneal opacities; scleral dermoids; eyelid colobomas; psychomotor retardation; seizures	Sporadic
Group 4: ACC overlying embryologic malformations	Abdomen, lumbar skin, scalp; any site	Meningomyeloceles; spinal dysraphia; cranial stenosis; congenital midline porencephaly; leptomeningeal angiomas; ectopia of ear; omphalocele; gastroschisis	Depends on underlying condition
Group 5: ACC with associated fetus papyraceus or placental infarcts	Multiple, symmetric areas, often stellate or linear, on scalp, chest, flanks, axillae, and extremities	Single umbilical artery; developmental delay; spastic paralysis; nail dystrophy; clubbed hands and feet; amniotic bands; gastrointestinal atresia	Sporadic
Group 6: ACC associated with EB: blistering, usually localized, without multiple congenital anomalies	Extremities	Blistering of skin and/or mucous membranes; absent or deformed nails; metatarsus varus; congenital absence of kidney (seen in cases of recessive, dystrophic EB; dominant, dystrophic EB; and EB simplex)	Depends on EB type: may be autosomal dominant or recessive
Junctional EB with pyloric atresia	Large areas on extremities and torso	Pyloric or duodenal atresia; abnormal ears and nose; ureteral stenosis; renal abnormalities; arthrogryposis	Autosomal recessive
Group 7: ACC localized to extremities without blistering	Pretibial areas; dorsal aspects of hands and feet; extensor areas of wrists	None	Autosomal dominant or recessive
Group 8: ACC caused by specific teratogens	Scalp (with methimazole); any area (with varicella and herpes simplex infections)	Imperforate anus (methimazole); signs of intrauterine infection with varicella and herpes simplex infections	Not inherited
Group 9: ACC associated with malformation syndromes (see also Table 9.2)	Scalp; any location	Trisomy 13; 4p– syndrome; many ectodermal dysplasias; Johanson–Blizzard syndrome; focal dermal hypoplasia; amniotic band disruption complex; XY gonadal dysgenesis	Varies, depending on specific syndrome

ACC, aplasia cutis congenita; EB, epidermolysis bullosa.

Modified from Frieden IJ. Aplasia cutis congenita: A clinical review and proposal for classification. *J Am Acad Dermatol* 1986; 14:646–660.

TABLE
9.2

Associated malformations and chromosomal defects reported with aplasia cutis

Syndrome	Clinical phenotype	Associated features	Inheritance
Opitz syndrome	Membranous aplasia cutis	Hypertelorism, cleft lip/palate, hypospadias, cryptorchidism	–
Adams–Oliver syndrome	Large, ill-defined, irregular scalp defects	Distal limb reduction abnormalities	Autosomal dominant
Oculocerebrocutaneous syndrome	Membranous aplasia cutis	Orbital cysts, cerebral malformations, facial skin tags, seizures, developmental delay	–
Trisomy D(13–15)	Membranous aplasia cutis	Holoprosencephaly, seizures, ocular abnormalities, deafness, neural tube defects	–
4p(-) syndrome	Not specified	Mental retardation, deafness, seizures, ocular abnormalities	–
Johanson–Blizzard syndrome	Small stellate defects of frontal scalp and membranous aplasia cutis	Dwarfism, mental retardation, deafness, hypothyroidism, pancreatic insufficiency	–
X-p22 microdeletion syndrome	Bilateral linear reticulated defects of the malar region of the face	Microphthalmia, sclerocornea	–
Chromosome 16–18 defect	Large scalp defects	Scalp arteriovenous malformation with underlying bony defect	–

TABLE
9.3

Correlation of clinical findings with proposed etiology and associations in aplasia cutis

Clinical phenotype	Proposed etiology	Associations
Cranial and facial membranous aplasia cutis	Developmental	Organoid nevi
Truncal, stellate aplasia cutis	Vascular disruption	Fetus papyraceus, placental insufficiency, gastrointestinal atresia
Extremity, angulated defects	Increased skin fragility	Epidermolysis bullosa
Small scar-like defects	Maternal infections	Varicella, herpes simplex virus infections
Cranial large, midline irregular defects	Developmental, genetic	Bone defects, hydrocephalus, arteriovenous fistula, sinus thrombosis
Reticulated facial lesions	Chromosomal abnormality	X-p22 deletion syndrome



Figure 9.22 Aplasia cutis with underlying bone defect in an infant with trisomy 13.



Figure 9.23 Membranous aplasia cutis with a subtle hair-collar sign.

configuration. The most common location is at the vertex of the scalp, but they may also be found anterior to the vertex, off the midline on the lateral parietal scalp, or even extending down onto the forehead along a line from the lateral forehead to the lateral edge of the eyebrows. Rarely, lesions of membranous aplasia cutis occur on the face, in a line extending from the preauricular region to the angles of the mouth.⁷⁶ The term focal facial dermal hypoplasia has been used to describe these lesions (Fig. 9.25). Lesions of temporal aplasia cutis may be associated with Setleis syndrome and found with additional

facial anomalies. Most reports of membranous aplasia cutis are sporadic, although there are well-documented patients with autosomal dominant and autosomal recessive patterns of inheritance.^{77,78} While the exact etiology of these lesions is unknown, the configuration, distribution, and clinical appearance would suggest incomplete closure of embryonic fusion lines, rather than vascular interruption or trauma to the skin.⁷⁶ A case of membranous aplasia cutis was detected by prenatal ultrasound at 27 weeks' gestation. A protruding, round, cystic lesion was noted at the vertex of the scalp. The lesion resolved

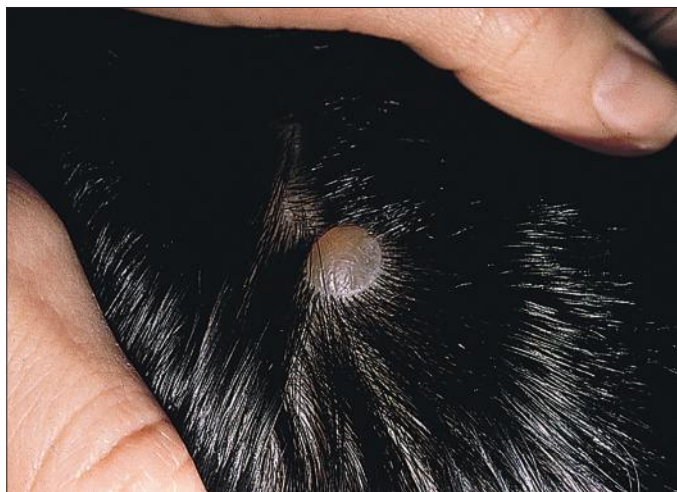


Figure 9.24 Bullous aplasia cutis in a newborn.



Figure 9.26 Large, irregular scalp defect of aplasia cutis.



Figure 9.25 Small, linear facial defects of aplasia cutis.



Figure 9.27 Truncal stellate aplasia cutis associated with fetus papyraceus.

spontaneously at 37 weeks' gestation, and a small oval lesion of membranous aplasia cutis was found in the identical location at birth.⁷⁹

Irregular, large (>3 cm), or stellate scalp defects of aplasia cutis are much less common, but may occur along the midline of the scalp (Fig. 9.26). These defects are more commonly familial and often associated with large underlying bony defects.⁸⁰ They have a high risk of infection and sagittal sinus thrombosis or hemorrhage. Abnormalities of the underlying venous system and arteriovenous malformations may be associated with these types of defects. Radiologic imaging with particular attention to the vasculature is recommended, as hemorrhagic complications and death have been reported.⁸¹

APLASIA CUTIS OF THE TRUNK

When the term 'aplasia cutis' is used in the most literal sense, this condition is found overlying abdominal malformations such as gastroschisis and omphalocele. Extensive truncal and limb defects have been associated with fetus papyraceus.^{82,83} These defects differ clinically from membranous aplasia cutis.

They are large, linear, or stellate erosions involving the lateral aspects of the trunk and extensor surfaces of the extremities (Fig. 9.27). Frequently, they are bilateral and symmetric. It is theorized that these defects are the result of placental infarction after the death of a twin fetus (Fig. 9.28), which would explain their symmetric distribution. These types of cutaneous lesions may also be associated with gastrointestinal malformations, particularly bowel atresia, which is also thought to be a consequence of early ischemia.⁸⁴ Additional extracutaneous findings include neurodevelopmental delay, intracranial hemorrhage, cardiac and arterial anomalies, renal cortical necrosis, and neonatal Volkmann ischemic contracture.^{85,86} Similar truncal defects have been seen in patients with pale or small placentas, and several have also been reported without mention of the placenta.⁸⁵ Irregular defects of the extremities and trunk have been reported with blistering of the skin (Bart syndrome); however, these are now considered to be a form of epidermolysis bullosa.^{75,87}

Reticulated linear skin defects of the malar region of the face have been reported as part of the X-p22 microdeletion syndrome (see Chapter 29). All reported cases have been female,

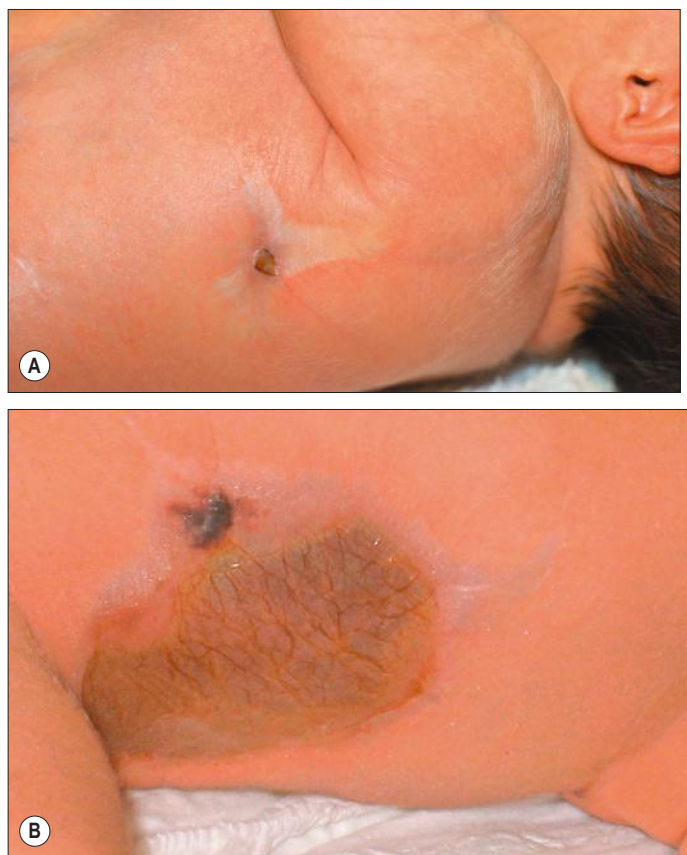


Figure 9.28 Stellate defect of aplasia cutis due to in-utero twin death.

suggesting that the deletion may be lethal in males. Severity varies in females from relatively mild facial scarring to major organ malformations. The syndrome is also associated with microphthalmia and sclerocornea.^{88–90}

Pathogenesis

Several theories have been proposed as to the etiology of aplasia cutis. Incomplete closure of the neural tube may explain midline lesions, and incomplete closure of embryonic fusion lines may explain the lateral membranous aplasia cutis lesions.⁷⁶ Vascular insufficiency to the skin may result from placental insufficiency or thrombotic material from a fetus papyraceus. Amniotic membrane adhesions, teratogenic agents, and intrauterine infections have also been implicated. Based on the heterogeneity of the associated findings, a unifying theory is unlikely.

Extracutaneous findings

Although ACC has been associated with several syndromes, the great majority of lesions occur as a solitary cutaneous finding. The lesions of membranous aplasia cutis most commonly occur as an isolated defect and usually require no further investigation. Even small underlying bony defects usually heal spontaneously. However, there are exceptions. Any lesion of aplasia cutis with a palpable lump within it should prompt further evaluation (see above). Midline lesions occurring at sites between the vertex and occiput are less common, and have a greater risk of underlying defects and/or sinus connections (Fig. 9.29). Larger lesions of aplasia cutis with large underlying bony

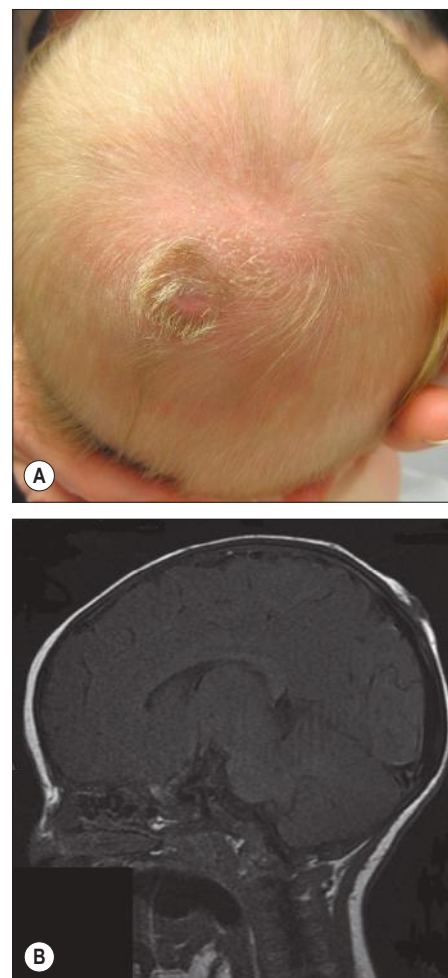


Figure 9.29 (A) Small, round, slightly elevated plaque of aplasia cutis of the occipital scalp with surrounding hair collar sign and a faint circumferential vascular stain. (B) MRI demonstrating soft tissue mass consistent with and an atretic meningocele.

defects need prompt imaging studies to assess for underlying CNS defects or connections, as well as evidence of close proximity to the sagittal sinus, as life-threatening hemorrhage has been reported in this setting and prompt surgical intervention may be required. These stellate or necrotic midline lesions have also been described in association with terminal transverse limb defects, the so-called Adams–Oliver syndrome. Familial cases of Adams–Oliver syndrome have been described and attributed to various mutations affecting cell-cell or cell-matrix. A very rare, distinctive subtype of aplasia cutis has been associated with X-p22 microdeletion syndrome. These infants have superficial and reticulate erosions over the bilateral cheeks and neck.⁹¹ Tables 9.2 and 9.3 list some of the associated malformations and chromosomal defects reported with aplasia cutis.⁹²

Diagnosis

The diagnosis is usually based on clinical data, although histologic examination of the defects may help to confirm the diagnosis. Membranous aplasia cutis has the most characteristic histologic findings; the epidermis is atrophic and flattened, and the normal superficial dermis is replaced by loose connective tissue.⁷⁶ The normal adnexal structures are small or completely

absent.⁹³ If a hair collar is present, then the edge of the specimen will have clustered, hypertrophic hair follicles. Other subtypes of aplasia cutis show superficial scarring with loss of normal adnexal structures. Increased levels of acetylcholinesterase and α -fetoprotein have been reported in the amniotic fluid of mothers with children with aplasia cutis.^{94,95}

Differential diagnosis

Postnatal trauma caused by forceps or monitoring devices, Goltz syndrome, epidermolysis bullosa, and incontinentia pigmenti can be confused with aplasia cutis.

Prognosis and management

If the lesion is ulcerated at birth, the area should be cleansed daily and a topical petrolatum-based ointment applied until complete healing has occurred. Secondary infection is uncommon except in cases of extensive scalp aplasia cutis. Small superficial skin ulcers usually heal in the first months of life. Similarly, small defects of the underlying bone usually ossify completely without treatment.⁹⁶ Most small defects will become inconspicuous as the child's scalp grows, but larger lesions may cause significant visible deformity, and almost all will result in localized alopecia. Surgical excision may be considered later in life. Lesions that are midline and posterior to the vertex of the scalp should be imaged to rule out a dermal sinus. If the defect is large, stellate in configuration, or associated with additional cutaneous abnormalities or bone defect, MRI should be considered before surgical resection.

Very large (>3 cm) stellate scalp defects (Fig. 9.26) can affect the galea, the pericranium, the bone, and the dura mater, and these lesions are at risk for infection and severe hemorrhage. They may take several months to heal and may require surgical intervention. In addition, these defects often have abnormalities of the intracranial vascular system. Consequently, radiologic investigation is indicated and required before surgical correction is undertaken because severe hemorrhage and even death has been reported after repair of large defects.^{97–100} The defects associated with fetus papyraceus heal remarkably well, leaving hypopigmented scars, and do not usually require surgical correction.

Cutaneous dimples

Cutaneous dimples are small depressions or pits in the skin that measure 1–4 mm. Dimples may occur at any location, but are more common over bony prominences such as the elbow, knee, acromion, and sacral region.¹⁰¹ Cutaneous dimples may be normal, particularly in some locations such as the face. Symmetric shoulder dimples over the acromion or supraspinous fossae may be familial and inherited in an autosomal dominant pattern.^{101–104} Cutaneous dimples have been associated with a wide variety of genetic disorders (Box 9.4).^{105–108} Dimples may be the result of aberrant fetal positioning in early gestation in patients with congenital skeletal dysplasia.¹⁰⁸ Lip dimples or lip pits may be an isolated defect or associated with Van der Woude syndrome, where they are bilateral, on the lower lip, and associated with cleft lip or palate (see Chapter 30). Usually, dimples do not require treatment, as they are small and not cosmetically disfiguring. Surgical excision may be indicated for lip dimples, as they can communicate with underlying minor salivary glands and have recurrent inflammation. Deep dimples in certain locations such as overlying the spine or on the buttock may actually



Figure 9.30 Adnexal polyp.

represent superficial manifestations of an underlying sinus tract, requiring evaluations, as discussed above.

Adnexal polyp

An adnexal polyp is a small, congenital papule found on the chest, usually on, or just medial to, the areola of the nipple. The lesions are small (1–2 mm), flesh-colored, firm, pedunculated papules with a smooth surface (Fig. 9.30). Older lesions may have a superficial crust. Histologically, the lesions are composed of adnexal structures. Hair follicles, vestigial sebaceous glands, and eccrine glands are present in the center of the lesion.¹⁰⁷ The lesions appear to fall off spontaneously soon after birth.

Developmental anomalies of the umbilicus

The umbilicus is a scar that represents the site of attachment of the umbilical cord in the fetus. The umbilical cord usually separates from the umbilicus at 1–8 weeks of life. Abnormal position of the umbilicus is often associated with other congenital abdominal wall defects such as omphalocele and gastroschisis. Persistent drainage or a mass at the site are signs of infection or persistent embryologic remnants.

ANOMALIES OF THE URACHUS

The urachus is the remnant of the regressed allantois running from the apex of the bladder to the umbilicus. If this structure fails to regress, leaving complete patency, a fistula forms between the bladder and the umbilicus. This is manifested by urine draining from the umbilicus. Partial patency of the urachus will result in a cystic dilation in which both ends are obliterated, forming an urachal cyst. Urachal cysts may occur at any point along the course of the urachus but do not communicate with the umbilicus or bladder. They present as tender, midline swellings between the umbilicus and the symphysis pubis. If the urachus is only patent at the umbilicus, an urachal sinus forms, which is usually associated with a proximal urachal cyst presenting as a cystic swelling at the umbilicus (Fig. 9.31).

BOX 9.4 GENETIC DISORDERS ASSOCIATED WITH CUTANEOUS DIMPLES

DIMPLES ASSOCIATED WITH ABERRANT POSITIONING DURING FETAL LIFE

- Arthrogryposis
- Metaphyseal chondrodysplasia
- Camptomelic dysplasia
- Kyphomelic dysplasia
- Mesomelic dysplasia
- Hypophosphatasia

FACIAL DIMPLES

- Cheeks
- Chin
- 'Whistling face' syndrome
- Simosa craniofacial syndrome
- Weaver syndrome

LIP DIMPLES

- Van der Woude syndrome
- Kabuki make-up syndrome
- Oral-facial-digital syndrome type 1
- Popliteal pterygium syndrome
- Branchio-oto-renal syndrome

SHOULDER DIMPLES

- Autosomal dominant dimples
- 18q deletion syndrome
- Trisomy 9p
- Russell-Silver syndrome
- Popliteal pterygium syndrome

PRETIBIAL DIMPLES

- Oral-facial-digital syndrome
- Osteoglyphonic syndrome
- Kyphomelic dysplasia

SACRAL DIMPLES

- Spina bifida
- Bloom syndrome
- Carpenter syndrome
- FG syndrome
- Robinow syndrome
- Smith-Lemli-Opitz syndrome
- Dubowitz syndrome
- Zellweger syndrome
- Wolf-Hirschhorn syndrome (4p deletion syndrome)
- X-linked dysmorphic syndrome with mental retardation

OTHER

- Maternal rubella syndrome
- Amniocentesis
- Joubert syndrome
- Caudal dysplasia sequence

ANOMALIES OF THE OMPHALOMESENTERIC DUCT

The omphalomesenteric duct connects the ileum to the umbilicus. This duct usually regresses during the 5th to 9th weeks' gestation, leaving a fibrous cord. Failure of normal obliteration will result in a range of congenital anomalies, depending on the extent and the site of persistent patency. The entire duct may be patent, forming a fistula between the ileum and the umbilicus; this presents during infancy with a red nodule at the umbilicus with a surrounding fistula. Fecal material may discharge from the fistula, often resulting in irritation of the surrounding skin. If intermediate portions of the duct remain patent, an



Figure 9.31 Urachal cyst.



Figure 9.32 Umbilical polyp (omphalomesenteric duct cyst).

omphalomesenteric cyst forms. If the cyst is located toward the periphery of the duct (i.e. near the umbilicus), it will give rise to a bright red, glistening polypoid nodule usually referred to as an umbilical polyp (Fig. 9.32). Meckel's diverticulum, the most common anomaly of the omphalomesenteric duct, results from incomplete regression of the most proximal (enteric) portion.

UMBILICAL GRANULOMA

Umbilical granulomas are small, red, broad-based, friable papules that develop if the umbilicus does not re-epithelialize completely; therefore they are not usually present at birth. They can be distinguished from umbilical polyps by the lack of serous, mucoid, or bloody discharge (Fig. 9.33), and their response to treatment with topical silver nitrate.

Prognosis and management

Umbilical granulomas can usually be treated with silver nitrate and are of little concern; however, these lesions may be difficult to clinically differentiate from congenital anomalies of the urachus and omphalomesenteric duct. In general, if the lesion is large, exophytic, and has a broad base (>0.5 cm), a referral to a pediatric general surgeon is indicated prior to treatment with silver nitrate.¹⁰⁹



Figure 9.33 Umbilical granuloma.



Figure 9.34 Multiple anomalies of the feet secondary to the amniotic band sequence.

Amnion rupture malformation sequence/amniotic bands

A variety of disorders result from premature rupture of the amniotic sac. The clinical features will vary depending on the stage of development of the fetus at the time of rupture.¹¹⁰ The defects are thought to result from early rupture of the amniotic membrane, which subsequently results in failure of the amniotic sac to grow and the formation of fibrous strands from the outer surface of the amnion and the chorion. The fetus may become entangled in these strands if it passes through the defect. There may also be compression of the fetus secondary to oligohydramnios. Maternal trauma, dietary deficiencies, and teratogens have all been associated with amniotic rupture sequence.

Cutaneous findings

The most classic cutaneous finding is a constriction band of the distal extremity (Fig. 9.34). The band is usually circumferential

and may be deep enough to cause lymphedema, compression of nerves, or even ischemia with resultant amputation.¹¹¹ Aplasia cutis, irregular patches of alopecia, abnormal palmar creases, and alteration in dermatoglyphic pattern are also cutaneous features of the amnion rupture malformation syndrome.

Extracutaneous findings

Rupture early in gestation, during organogenesis, will lead to the most severe deformities. Severe craniofacial abnormalities, such as neural tube defects, and facial, chest, and abdominal wall clefts, have all been reported.

Treatment

Surgical correction is the only treatment option for these deformities and is often very challenging.¹¹²

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KEY REFERENCES

30. Golden JA, Chernoff GF. Multiple sites of anterior neural tube closure in humans: evidence from anterior neural tube defects (anencephaly). *Pediatrics* 1995;95:506–10.
35. Drolet B, Prendiville J, Golden J, et al. Membranous aplasia cutis with hair collars: Congenital absence of the skin or neuroectodermal defect? *Arch Dermatol* 1995;131:1427–9.
42. Albright A, Gartner J, Weiner E. Lumbar cutaneous hemangiomas as indicators of tethered spinal cords. *Pediatrics* 1989;83:977–80.
55. Goldberg N, Hebert A, Esterly N. Sacral hemangiomas and multiple congenital abnormalities. *Arch Dermatol* 1986;122:684–7.
57. Drolet BA, Chamlin SL, Garzon MC, et al. Prospective study of spinal anomalies in children with infantile hemangiomas of the lumbosacral skin. *J Pediatr* 2010;157(5):789–94.
75. Frieden IJ. Aplasia cutis congenita: A clinical review and proposal for classification. *J Am Acad Dermatol* 1986;14:646–60.
86. Leaute-Lebreze C, Depaire-Duclos F, Sarlangue J, et al. Congenital cutaneous defects as complications of surviving co-twins; aplasia cutis congenita and neonatal Volkmann ischemic contracture of the forearm. *Arch Dermatol* 1998;134:1121–4.

REFERENCES

- Armoni M, Filk D, Schlesinger M, et al. Accessory nipples: any relationship to urinary tract malformation? *Pediatr Dermatol* 1992;9:239–40.
- Mimouni F, Merlob P, Reisner SH. Occurrence of supernumerary nipples in newborns. *Am J Dis Child* 1983;137:952–3.
- Cohen PR. The significance of polythelia. *J Am Acad Dermatol* 1995;32:688.
- Meggyessy V, Mehes K. Association of supernumerary nipples and renal anomalies. *J Pediatr* 1987;111:412–13.
- Urbani CE, Betti R. Accessory mammary tissue associated with congenital and hereditary nephrourethral malformations. *Int J Dermatol* 1996;35:349–52.
- Grotto I, Browner-Elhanan K, Mimouni D, et al. Occurrence of supernumerary nipples in children with kidney and urinary tract malformations. *Pediatr Dermatol* 2001;18:291–4.
- Hrabovszky T, Schneider I, Zombai E. Axillare akzessorische brust drusen. [Axillary accessory breast tissue]. *Hautarzt* 1995;46:576–8.
- Kao GF, Graham JH, Helwig EB. Paget's disease of the ectopic breast with an underlying intraductal carcinoma: A report of a case. *J Cutan Pathol* 1986;13:59–66.
- Jacobs PH, Shafer JC, Higdon RS. Congenital branchiogenic anomalies. *J Am Med Assoc* 1959;169:442–6.
- Leung AK, Robson WL. Association of preauricular sinuses and renal anomalies. *Urology* 1992;40:259–61.
- Wang RY, Earl DL, Ruder RO, et al. Syndromic ear anomalies and renal ultrasounds. *Pediatrics* 2001;108:32–9.
- Kugelman A, Hadad B, Ben-David J, et al. Preauricular tags and pits in newborn: The role of hearing tests. *Acta Pediatr* 1997;86:170–2.
- Resnick KI, Soltani K, Bernstein JE, et al. Accessory tragi and associated syndromes involving the first branchial arch. *J Dermatol Surg Oncol* 1981;7:39–41.
- Zelante L, Gasparini P, Scanderbeg AC, et al. Goldenhar complex: A further case with uncommon associated anomalies. *Am J Med Genet* 1997;69:418–21.
- Satoh T, Tokura Y, Katsumata T, et al. Histologic diagnostic criteria for accessory tragi. *J Cutan Pathol* 1990;17:206–10.
- Frieden IJ, Chang MW, Lee I. Suture ligation of supernumerary digits and 'tags': An outmoded practice? *Arch Pediatr Adolesc Med* 1995;149:1284.
- Sperling LC. Congenital cartilaginous rests of the neck. *Int J Dermatol* 1986;3:186–7.
- Hogan D, Wilkinson RD, Williams. Congenital anomalies of the head and neck. *Int J Dermatol* 1980;19:479–86.
- Maran AG, Buchanan DR. Branchial cysts, sinuses and fistulae. *Clin Otolaryngol* 1978;3:77–92.
- Ahuja AT, Wong KT, King AD, et al. Imaging for thyroglossal duct cysts: the bare essentials. *Clin Radiol* 2005;60:141–8.
- Muramatsu T, Shirai T, Sakamoto K. Cutaneous bronchogenic cyst. *Int J Dermatol* 1990;29:143–4.
- Jona JZ. Extramediastinal bronchogenic cysts in children. *Pediatr Dermatol* 1995;12:304–6.
- Patterson JW, Pittman DL, Rich JD. Prester-nal ciliated cyst. *Arch Dermatol* 1984;120:240–2.
- Asarch RG, Golitz LE, Sausker WF, et al. Median raphe cysts of the penis. *Cutis* 1981;27:170–2.
- Carmi R, Boughman JA. Pentalogy of Cantrell and associated midline anomalies: A possible ventral midline developmental field. *Am J Med Genet* 1992;42:90–5.
- Hersh JH, Waterfill D, Rutledge J, et al. Sternal malformation/vascular dysplasia association. *Am J Med Genet* 1985;21:117–86.
- Kaplan LC, Kurnit DM, Welch KJ. Anterior midline defects: Association with ectopic cordis or vascular dysplasia, defines two distinct entities. *Am J Med Genet* 1985;21:203.
- Gargon R, McKinnon M, Mulliken J. Midline cervical cleft. *Plast Reconstruct Surg* 1985;76:226–9.
- Eastlack JP, Howard RM, Frieden IJ. Congenital midline cervical cleft: case report and review of the English language literature. *Pediatr Dermatol* 2000;17:118–22.
- Golden JA, Chernoff GF. Multiple sites of anterior neural tube closure in humans: evidence from anterior neural tube defects (anencephaly). *Pediatrics* 1995;95:506–10.
- Peter J, Sinclair-Smith C, deVilliers J. Midline dermal sinuses and cysts and their relationship to the central nervous system. *Eur J Pediatr Surg* 1991;1:73–9.
- Powell K, Cherry J, Hougen T, et al. A prospective search for congenital dermal abnormalities of the craniospinal axis. *J Pediatr* 1975;87:744–50.
- Commens C, Rogers M, Kan A. Heterotopic brain tissue presenting as bald cysts with a collar of hypertrophic hair; the hair collar sign. *Arch Dermatol* 1989;125:1253–6.
- Drolet B, Clowry L Jr, McTigue K, et al. The hair collar sign: A cutaneous marker for neural tube dysraphism. *Pediatrics* 1995;96:309–13.
- Drolet B, Prendiville J, Golden J, et al. Membranous aplasia cutis with hair collars: Congenital absence of the skin or neuroectodermal defect? *Arch Dermatol* 1995;131:1427–9.
- Howard R. Congenital midline lesions: Pits and protuberances. *Pediatr Ann* 1998;27:150–60.
- Nocini P, Barbaglio A, Dolci M, et al. Dermoid cyst of the nose: A case report and review of the literature. *J Oral Maxillofac Surg* 1996;54:357–62.
- Paller AS, Pensler J, Tomita T. Nasal midline masses in infants and children. Dermoids, encephaloceles, and nasal gliomas. *Arch Dermatol* 1991;127:362–6.
- Martinez-Lage JE, Capel A, Costa TR, et al. The child with a mass on its head: Diagnostic and surgical strategies. *Childs Nerv Syst* 1992;8:247–52.
- Hattori H, Higuchi Y, Tashiro Y. Dorsal dermal sinus and dermoid cysts in occult spinal dysraphism. *J Pediatr* 1999;134:793.
- Kriss T, Kriss V, Warf B. Recurrent meningitis: The search for the dermoid or epidermoid tumor. *Pediatr Infect Dis J* 1995;14:697–700.
- Albright A, Gartner J, Weiner E. Lumbar cutaneous hemangiomas as indicators of tethered spinal cords. *Pediatrics* 1989;83:977–80.
- Higginbottom M, Jones K, James H, et al. Aplasia cutis congenita: A cutaneous marker of occult spinal dysraphism. *J Pediatr* 1980;96:687–9.
- Anderson F. Occult spinal dysraphism: A series of 73 cases. *Pediatrics* 1975;55:826–35.
- Assaad A, Mansy A, Kotb M, et al. Spinal dysraphism: Experience with 250 cases operated upon. *Childs Nerv Syst* 1989;5:324–9.
- Burrows F. Some aspects of occult spinal dysraphism: A study of 90 cases. *Br J Radiol* 1968;41:487–91.
- Hall D, Udvarhelyi G, Altman J. Lumbosacral skin lesions as markers of occult spinal dysraphism. *JAMA* 1981;246:2606–8.
- Lemire R, Graham C, Beckwith J. Skin-covered sacrococcygeal masses in infants and children. *J Pediatr* 1971;79:948–54.
- Sattar M, Bannister C, Turnbull I. Occult spinal dysraphism – the common combination of lesions and the clinical manifestations in 50 patients. *Eur J Pediatr Surg* 1997;6:10–14.
- Scatliff J, Kendall B, Kingsley D, et al. Closed spinal dysraphism: Analysis of clinical, radiological and surgical findings in 104 consecutive patients. *Am J Roentgenol* 1989;10:269–77.
- Tavafoghi V, Ghandchi A, Hambrick G, et al. Cutaneous signs of spinal dysraphism: report of a patient with a tail-like lipoma and review of 200 cases in the literature. *Arch Dermatol* 1978;114:573–7.
- Keim HA, Greene AF. Diastematomyelia and scoliosis. *J Bone Joint Surg Am* 1973;55:1425–34.
- Guggisberg D, Hadj-Rabia S, Viney C, et al. Skin markers of occult spinal dysraphism in children: a review of 54 cases. *Arch Dermatol* 2004;140:1109–15.
- Karrer F, Flannery A, Nelson M, et al. Anorectal malformations. Evaluation of associated spinal dysraphic syndromes. *J Pediatr Surg* 1988;23:45–8.
- Goldberg N, Hebert A, Esterly N. Sacral hemangiomas and multiple congenital abnormalities. *Arch Dermatol* 1986;122:684–7.
- Rivosecchi M, Luchetti M, Zaccara A, et al. Spinal dysraphism detected by MRI in patients with anorectal abnormalities: Incidence and clinical significance. *J Pediatr Surg* 1995;30:383–8.
- Drolet BA, Chamlin SL, Garzon MC, et al. Prospective study of spinal anomalies in children with infantile hemangioma of the lumbosacral skin. *J Pediatr* 2010;157(5):789–94.
- Schumacher WE, Drolet BA, Maheshwari M, et al. Spinal dysraphism associated with the cutaneous lumbosacral infantile hemangioma: a neuroradiological review. *Pediatr Radiol* 2011;42:315–20.
- Enjolras O, Boukobza M, Jdid R. Cervical occult spinal dysraphism: MRI findings and the value of a vascular birth mark. *Pediatr Dermatol* 1995;12:256–9.
- Ben-Amitai D, Davidson S, Schwartz M, et al. P16 The role of imaging in the evaluation of sacral nevus flammeus simplex: A prospective neonatal study. *Eur J Pediatr Dermatol Int Congress Dermatol* 1998;8:40.
- Kriss VM, Desal NS. Occult spinal dysraphism in neonates: Assessment of high-risk cutaneous stigmata on sonography. *Am J Roentgenol* 1998;171:1687–92.
- McAtee-Smith J, Hebert A, Rapini R, et al. Skin lesions of the spinal axis and spinal dysraphism. *Arch Pediatr Adolesc Med* 1994;148:740–8.
- Harrist T, Gang D, Kleinman G, et al. Unusual sacrococcygeal embryologic malformations with cutaneous manifestations. *Arch Dermatol* 1982;118:643–8.

64. Weprin BE, Oakes WJ. Coccygeal pits. *Pediatrics* 2000;105:69–73.
65. Carrillo R, Carreira LM, Prada JJ, et al. Lateral congenital spinal dermal sinus. A new clinical entity. *Childs Nerv Syst* 1985;1:238–40.
66. Dao A, Netsky M. Human tails and pseudo-tails. *Hum Pathol* 1984;15:449–53.
67. Chern JJ, Aksut B, Kirkman JL, et al. The accuracy of abnormal lumbar sonography findings in detecting occult spinal dysraphism: a comparison with magnetic resonance imaging. *J Neurosurg Pediatr* 2012;10(2):150–3.
68. Barnes P, Lester P, Yamanashi W, et al. Magnetic resonance imaging in infants and children with spinal dysraphism. *Am J Neuroradiol* 1986;7:465–72.
69. Byrd S, Darling C, Melone D, et al. MR imaging of the pediatric spine. *Magn Reson Imag Clin North Am* 1996;4:797–833.
70. Rindahl M, Colletti P, Zee C, et al. Magnetic resonance imaging of pediatric spinal dysraphism. *Magn Reson Imag* 1989;7:217–24.
71. Tracy P, Hanigan W. Spinal dysraphism: Use of magnetic resonance imaging in evaluation. *Clin Pediatr* 1990;29:228–33.
72. Raghavendra B, Epstein F, Pinto R, et al. The tethered spinal cord: Diagnosis by high-resolution real time ultrasound. *Radiology* 1983;149:123–8.
73. Rohrschneider U, Forsting M, Darge K, et al. Diagnostic value of spinal ultrasound: Comparative study with MR imaging in pediatric patients. *Radiology* 1996;200:383–8.
74. Myer BJ, Tercier S, Lutz N, et al. Introduction of a urodynamic score to detect pre- and post-operative neurological deficits in children with a primary tethered cord. *Childs Nerv Syst* 2003;19:716–21.
75. Frieden IJ. Aplasia cutis congenita: A clinical review and proposal for classification. *J Am Acad Dermatol* 1986;14:646–60.
76. Drolet BA, Baselga E, Gosain AK, et al. Preauricular skin defects: A consequence of a persistent ectodermal groove. *Arch Dermatol* 1997;133:1551–4.
77. Pap GS. Congenital defect of the scalp and skull in three generations of one family. *Plast Reconstruct Surg* 1970;46:194–6.
78. Sybert V. Aplasia cutis congenita. A report of 12 new families and review of the literature. *Pediatr Dermatol* 1985;3:1–14.
79. Cambiagli S, Gelmetti C, Nicolini U. Prenatal findings in membranous aplasia cutis. *J Am Acad Dermatol* 1998;39:638–40.
80. Baselga E, Torrelo A, Drolet BA. Familial non-membranous aplasia cutis of the scalp. *Pediatr Dermatol* 2005;22:213–17.
81. Singman R, Asaikan S, Hotson G, et al. Aplasia cutis congenita and arteriovenous fistula. *Arch Neurol* 1990;47:1255–8.
82. Saier F, Burden L, Cavanagh D. Fetus papyraceus: An unusual case with congenital anomaly of the surviving fetus. *Obstet Gynecol* 1975;45:217–20.
83. Mannino F, Jones K, Benirschke K. Congenital skin defects and fetus papyraceus. *J Pediatr* 1977;91:559–64.
84. Branspiegel N. Aplasia cutis congenita and intestinal lymphangiectasia: an unusual association. *Am J Dis Child* 1985;139:509–13.
85. Dowler VB. Congenital defect of the skin in a newborn infant. *Am J Dis Child* 1932;44:1279–84.
86. Leaute-Lebreze C, Depaire-Duclos F, Sarlangue J, et al. Congenital cutaneous defects as complications of surviving co-twins; aplasia cutis congenita and neonatal Volkmann ischemic contracture of the forearm. *Arch Dermatol* 1998;134:1121–4.
87. Bart B, Garlin R, Anderson V, et al. Congenital absence of the skin and associated abnormalities resembling epidermolysis bullosa. *Arch Dermatol* 1966;93:296–304.
88. Al-Gazali LI, Mueller RF, Caine A, et al. Two 46,XX,t(X;Y) females with linear skin defects and congenital microphthalmia: a new syndrome at Xp22.3. *J Med Genet* 1990;27:59–63.
89. Temple IK, Hurst JA, Hing S, et al. De novo deletion of Xp22.2-pter in a female with linear skin lesions on the face and neck, microphthalmia, and anterior chamber eye anomalies. *J Med Genet* 1990;27:56–8.
90. Allanson J, Richter S. Microphthalmia: A new syndrome at Xp22.2. *J Med Genet* 1991;28:143–4.
91. Shaheen R, Aglan M, Keppler-Noreuil K, et al. Mutations in EOGT confirm the genetic heterogeneity of autosomal-recessive Adams-Oliver syndrome. *Am J Hum Genet* 2013;92(4):598–604.
92. Evers MJ, Steijlen PM, Hamel BJ. Aplasia cutis congenita and associated disorders: An update. *Clin Genet* 1995;47:295–301.
93. Lever WF. Aplasia cutis. In: Lever WF, Schaumburg-Lever G, editors. *Histopathology of the skin*. 7th ed. Philadelphia: JB Lippincott; 1990. p. 65–6.
94. Farine D, Maidman J, Rubin S, et al. Elevated alpha-fetoprotein in pregnancy complicated by aplasia cutis after exposure to methimazole. *Obstet Gynecol* 1988;71:996–7.
95. Bick DP, Balkite MS, Baumgarten JC, et al. The association of congenital skin disorders with acetylcholinesterase in amniotic fluid. *Prenat Diagn* 1987;7:543–9.
96. Wexler A, Harris M, Lesavoy M. Conservative treatment of cutis aplasia. *Plast Reconstruct Surg* 1990;86:1066–71.
97. Glasson DW, Duncan GM. Aplasia cutis congenita: Delayed closure complicated by massive hemorrhage. *Plast Reconstruct Surg* 1985;75:423–5.
98. Schneider BM, Berg RA, Kaplan AM. Aplasia cutis complicated by sagittal sinus thrombosis. *Pediatrics* 1980;66:948–50.
99. Harvey G, Solanki NS, Anderson PJ, et al. Management of aplasia cutis congenita of the scalp. *J Craniofac Surg* 2012;23(6):1662–4.
100. Maillet-Declerck M, Vinchon M, Guerreschi P, et al. Aplasia cutis congenita: review of 29 cases and proposal of a therapeutic strategy. *Eur J Pediatr Surg* 2013;23(2):89–93.
101. Samlaska CP. Congenital supraspinous fossae. *J Am Acad Dermatol* 1991;25:1078–9.
102. Weidemann HR. Cheek dimples. *Am J Med Genet* 1990;36:376.
103. Biachine JW. Acromial dimples: A benign familial trait. *Am J Hum Genet* 1974;26:412–13.
104. Wood VE. Congenital skin fossae about the shoulder. *Plast Reconstruct Surg* 1990;85:798–800.
105. DiRocco M. On Saraiva and Baraister and Joubert syndrome: A review. *Am J Med Genet* 1993;46:732–3.
106. Jones KL. Smith's recognizable patterns of human malformations. 4th ed. Philadelphia: WB Saunders; 1988. p. 42–4, 94–5, 104–15, 178–9, 182–3, 240–1, 370–1, 575–6.
107. Squires LA, Raymond G, Neumeyer AM, et al. Dysmorphic features of Joubert syndrome. *Dysmorph Clin Genet* 1991;5:72.
108. Kozłowski K, Baca L, Brachimi L, et al. Mesomelic dysplasia of the upper extremities associated with other abnormalities: A new syndrome? *Pediatr Radiol* 1993;23:108–10.
109. Kondrich J, Woo T, Ginsburg HB, et al. Evisceration of small bowel after cauterization of an umbilical mass. *Pediatrics* 2012;130(6):e1708–10.
110. Rossillon D, Rombouts JJ, Verellen-Dumoulin C, et al. Congenital ring-constriction syndrome of the limbs; a report of 19 cases. *Br J Plast Surg* 1988;41:270–7.
111. Hidano A, Kobayashi T. Adnexal polyp of neonatal skin. *Br J Dermatol* 1975;92:659.
112. Higginbottom MC, Jones KL, Hall BD, et al. The amniotic band disruption complex: Timing of amniotic rupture and variable

Vesicles, Pustules, Bullae, Erosions, and Ulcerations

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Introduction

Vesiculopustular and bullous disorders are common in the neonatal period and the first years of life. Accurate and prompt diagnosis is essential because some conditions that present with blisters and pustules are truly life-threatening. In contrast, many others are innocuous and self-limited; misdiagnosis of a more serious condition can lead to iatrogenic complications, unnecessary expense, and parental anguish.

The causes of blisters and pustules in newborns and young infants are influenced by the clinical setting, including geography and whether patients are seen in a hospital or clinic. Infection is the most common etiology in developing countries. In a study of neonates in India with blisters and pustules, bacterial infection was the most common overall, whereas erythema toxicum was the most prevalent non-infectious etiology.¹ In a prospective study of newborn inpatients in California examined by pediatric dermatologists, the most common eruption in newborns was erythema toxicum.² In a retrospective European study done in a Level 3 nursery, vesicles and pustules were the sole reason for admission to the Neonatal Intensive Care Unit (NICU) in 29.8% of infants admitted because of skin lesions.³

Several articles have reviewed an approach to infants with these cutaneous findings,^{4–6} including infants with hemorrhagic vesiculopustules.⁷ There is also considerable overlap with the subject matter in other chapters of this book, most notably [Chapter 7](#) (Transient Benign Cutaneous Lesions in the Newborn), and [Chapters 12, 13 and 14](#) (Bacterial, Viral, and Fungal Infections, respectively), so the main discussion of specific disorders are discussed therein. [Chapter 11](#) discusses the diagnosis and management of epidermolysis bullosa and other non-infectious causes of bullae, so those conditions are covered in far less detail in this chapter.

In addition to a discussion of vesicles, pustules and bullae, this chapter also includes conditions presenting with erosions and ulcerations. Although vesicles, pustules, and bullae are *primary* skin lesions, they can quickly progress to *secondary* skin lesions (i.e. erosions and ulcerations). This can occur rapidly or have transpired in utero, such that erosions and ulcerations are the main presenting finding. Examples include staphylococcal scalded skin syndrome, where erythema and skin erosions predominate over blisters, and *Pseudomonas* skin infection, where pustules rapidly evolve into necrotic ulcers.

Because of the wide range of diagnoses discussed in this chapter, there are boxes and tables to help with a systematic approach to evaluation and differential diagnosis. [Tables 10.1–10.3](#) summarize key findings and differential diagnosis of vesiculopustular diseases in newborns and infants, including infectious causes, relatively common transient skin lesions, and uncommon and rare causes of this clinical presentation. [Tables 10.4–10.6](#) summarize these same categories for the differential

diagnosis of bullae, erosions, and ulcerations. [Box 10.1](#) lists conditions in neonates where pustules and vesicles predominate, [Box 10.2](#) lists the conditions in neonates where bullae predominate, and [Box 10.3](#) lists conditions in neonates where erosions or ulcerations may predominate.

Bacterial infections (see Chapter 12)

STAPHYLOCOCCUS AUREUS INFECTIONS

Skin infections caused by *S. aureus* are relatively common in newborns and infants. Epidemic outbreaks are occasionally seen in newborn and intensive care nurseries.^{8–10} In recent years, methicillin-resistant *S. aureus* (MRSA) infections have been increasingly reported in hospital nursery and maternity units, paralleling a trend toward such infections in other settings. Interestingly, most have had the molecular fingerprint of community-acquired (CA-MRSA), rather than nosocomial MRSA.^{5,8,9} Two forms of *S. aureus* infection involving the skin can occur: direct skin infection and staphylococcal scalded skin syndrome, caused by staphylococcal toxins.

STAPHYLOCOCCUS AUREUS PYODERMA

Superficial skin infections with *S. aureus* (staphylococcal pyoderma) can result in crusted impetigo, bullous impetigo, and pustular folliculitis ([Figs 10.1, 10.2](#)). Deeper skin infections can result in furunculosis, cellulitis, and abscesses. Infection is virtually never present at birth, but develops in the first days to weeks of life. It typically presents with discrete vesicles and pustules. Toxin-producing *S. aureus* can present with tense, fragile vesicles and bullae. As these rupture, they may often leave either moist superficial erosions or crusted areas with a collarette of scale ([Fig. 10.3](#)). Superficial staphylococcal infection can also present with crusted impetigo without clinically obvious vesicles, pustules, or bullae.¹¹

Common sites of involvement include the neck folds, diaper area, and axillae. More extensive cases of generalized bullous impetigo are occasionally seen.¹² The patients are usually otherwise well, without signs of more generalized infection. In two reports of CA-MRSA outbreaks in a well-baby nursery, neonates presented in the first 2.5 weeks of life with discrete pustules often in the diaper area but also on the trunk or posterior auricular surface; two babies had cellulitis. The skin lesions cleared rapidly with topical and/or oral antimicrobials.^{8,9}

In older infants, superficial infection can progress to invasive disease, especially in the malnourished or otherwise compromised host. In one study in India, 26% of pediatric patients with invasive staphylococcal disease had a preceding history of pustules.¹³ Staphylococcal infection can also cause a persistent perianal rash that involves the buttocks, in contrast to more localized

TABLE 10.1 Differential diagnosis of vesiculopustular diseases in newborns and infants – Infectious causes

Disease	Usual age of onset	Skin: morphology	Skin: usual distribution	Clinical: other	Diagnosis/findings
Staphylococcal pyoderma	Neonatal through infancy	Pustules, bullae, occasionally vesicles; crusted impetigo, folliculitis with follicular-based papules, pustules or furuncles	Any site: in neonates often concentrated in the diaper area and periumbilical skin. Infants: anywhere but often in fold areas, around mouth and nose. Perianal erythema similar to perianal <i>Strep</i> .	If toxin-producing <i>S. aureus</i> may occur in epidemics. In this setting, often collarettes of scale at periphery	Gram stain: PMNs Gram-positive cocci in clusters. Bacterial culture
Group A streptococcal infection	Neonatal through infancy	Isolated pustules, honey-crusted areas, bullae, moist erythema. Perianal erythema with or without fissures, erosions or pustules. Blistering distal dactylitis	Any site including palms, soles. In older infants characteristic presentations may include blistering distal dactylitis on volar fingertips; perianal 'dermatitis'	Rare in neonates but may have other findings suggesting sepsis. Infants may have fever or other signs of systemic infection (more than with <i>S. aureus</i>), positive history of exposure to <i>Strep</i> . throat in family member	Gram stain: Gram-positive cocci in chains; bacterial culture, rapid <i>Strep</i> . test. In older children throat culture may also be positive
Group B streptococcal infection (GBS)	In neonates – rare. In infants uncommon but similar to Group A <i>Strep</i> . infection	Vesicles bullae, erosions, honey-crusted lesions	Any area including perianal and distal dactylitis	Neonates may have GBS systemic infection. In older children GBS is not always a pathogen – can represent colonization	Gram stain: Gram-positive cocci in chains; bacterial culture
Listeriosis	Birth, first few hours	Hemorrhagic pustules and petechiae	Generalized, especially trunk and extremities	Sepsis; respiratory distress; maternal fever; preterm labor	Gram-positive rods; bacterial culture skin and other sites
<i>Haemophilus influenzae</i> infection	Birth or first few days	Vesicles, crusted areas	No specific site predisposed	Bacteremia, meningitis may be present	Gram-negative bacilli; bacterial culture
<i>Pseudomonas</i> infection	Days to weeks. Later onset months to years	Erythema, pustules, hemorrhagic bullae, necrotic ulcerations	Any area, but especially diaper, periorificial	History of illness in neonatal period, immunocompromised host; occasionally immunocompetent infant	Skin or tissue Gram stain: Gram-negative rods; cultures skin, blood
Congenital and neonatal candidiasis	Birth or first few days of life	Erythema, small papules and pustules. Burn-like dermatitis with scaling may develop in extremely premature infants even after a few weeks of life	Any part of body; upper torso, palms, soles often involved	Risk factors include prematurity. Foreign body in cervix/uterus	KOH: hyphae, budding yeast; placental lesions. Skin culture can grow on standard bacterial media. Skin biopsy may be helpful if KOH negative
<i>Candida albicans</i> infection	Neonates and infants	Usual: Beefy red patches with overlying fine scale, satellite papules and pustules. Less common: moist erythema in folds	Diaper or other intertriginous area	Usually otherwise healthy	KOH: hyphae, budding yeast if pustules are present
<i>Aspergillus</i> infection	Few days to weeks	Pustules often clustered, rapidly evolve to ulcers	Any area	Extreme prematurity usually present	Skin biopsy: septate hyphae; tissue fungal culture

Intrauterine herpes simplex	Birth; first few days of life	Vesicles, pustules, widespread erosions, congenital scars, areas of missing skin	Any site but scalp often affected with aplasia cutis-like areas	Signs of TORCH infections, e.g., low-birthweight; microcephaly, chorioretinitis	Tzanck; FA or immunoperoxidase slide test, PCR, viral culture
Neonatal herpes simplex	Usually 5–14 days	Vesicles, pustules, crusts, erosions	Any site; especially scalp, torso; may involve mucosa	Signs of sepsis; irritability, lethargy	Tzanck; FA or immunoperoxidase slide test, PCR, viral culture
Herpes simplex infection: older infants	Weeks to years	Primary gingivostomatitis. Recurrent HSV	Intra- and perioral vesicles erosions and erythema	Fever, irritability, adenopathy if primary. Often recurs in same site, sun exposure may provoke.	Tzanck; FA or immunoperoxidase slide test, PCR, viral culture
		Eczema herpeticum: erosions, small vesicles and punched-out erosions	Often face but any site – pattern may be grouped in some areas but trail off in others	In setting of atopic dermatitis, usual moderate to severe.	
		Herpetic whitlow: grouped vesicles, pustules or bullae	Acral skin, usually finger or toe	May mimic bacterial dactylitis	
Neonatal varicella	0–14 days	Vesicles on erythematous base; Lesions usually in same stage of development	Generalized distribution, often much more widespread than outside newborn period	Maternal primary varicella infection 7 days before to 2 days after delivery	Tzanck, FA, viral culture
Herpes zoster	Neonates and infants	Vesicles on erythematous base in dermatomal pattern	Typically extremity or torso	Maternal primary varicella infection during pregnancy OR primary varicella early in life	Tzanck, FA, viral culture
Primary varicella (Chickenpox)	Weeks to years	Crops of lesions at varying stages. Vesicles on erythematous base	Often starts on scalp, with accentuation of torso, but can be generalized	More common in unimmunized infants but can occur in less pronounced form in immunized infants (usually less vesicular)	Tzanck, FA, viral culture
Enteroviral exanthems	Weeks to years	Hand, foot, mouth: oval gray vesicles; Other enteroviral exanthems: Small vesicles, bullae, eczema herpeticum-like petechial	Intraoral; Acral distribution with accentuation of palms, soles, diaper area	Occasionally fever, vomiting, diarrhea, upper respiratory symptoms; Skin pain or itch; Several weeks later: onychomadesis	PCR or viral culture: best yield are nasopharynx, rectum, vesicular skin lesions
Scabies	Usually 3–4 weeks or older	Multiple morphologies in the same patient i.e., papules, wheals, nodules, crusted areas, vesicles, burrows	Accentuated axillae, feet, wrists, may occur anywhere	Pruritus. Usually family members with itching, rash	Scabies prep demonstrating mites, eggs, or feces; clinical
Chikungunya virus	Infants, weeks to years	Vesicles or bullae	Generalized	Epidemics in developing countries; Fever	

TABLE
10.2

Differential diagnosis of vesiculopustular diseases – Transient skin lesions

Disease	Usual age of onset	Skin: morphology	Skin: usual distribution	Clinical: other	Diagnosis/findings
Erythema toxicum neonatorum	Usually 24–28 h, but can be birth to 2 weeks	Erythematous macules, papules, pustules, wheals	Anywhere except palms, soles	Term infants >2500 g	Clinical; Wright's stain: eosinophils
Neonatal pustular melanosis	Birth or shortly thereafter but collarettes of scale or hyperpigmented macules occasionally noted at a few days to weeks; not at birth	Pustules without underlying erythema; collarettes of scale; hyperpigmented macules; lesions may be clustered together	Anywhere; most often forehead, ears, back, fingers, toes	Term infants; more common in black infants	Clinical; Wright's stain: PMNs, occasional eosinophil, cellular debris
Miliaria crystallina	Birth, neonatal period or later in infancy	Fragile vesicles without underlying erythema	Forehead, upper trunk, arms most common	Can be congenital but in acquired cases typically a history of fever	Clinical; Wright, Gram and Tzanck preps negative
Miliaria rubra	Neonatal or infancy	Erythematous papules with superimposed pustules typically concentrated in one or two areas; not generalized	Forehead, upper trunk, arms most common	Sometimes history of overwarming, fever, or use of occlusive dressing or garment	Clinical; Wright, Gram and Tzanck preps negative
Neonatal 'acne' (benign cephalic pustulosis)	Days to weeks	Papules and pustules on erythematous base	Cheeks, forehead, eyelids, neck, upper chest, scalp	Otherwise well; may have scaling in scalp	Usually clinical; Giemsa: negative or fungal spores, neutrophils

BOX 10.1 CONDITIONS IN NEONATES WHERE PUSTULES AND/OR VESICLES PREDOMINATE

COMMON CAUSES

- Neonatal candidiasis^a
- Herpes simplex^a
- Superficial staphylococcal infection^a
- Erythema toxicum neonatorum
- Neonatal pustular melanosis
- Neonatal 'acne' (benign cephalic pustulosis)
- Miliaria crystallina and rubra

UNCOMMON CAUSES

- Congenital candidiasis^a
- Herpes simplex^a
- Scabies^a
- Acropustulosis of infancy
- Incontinentia pigmenti

RARE CAUSES

- *Aspergillus*^a
- Chikungunya virus^a
- Cytomegalovirus^a
- Group B streptococcus^a
- Group A streptococcus^a
- *H. influenza*^a
- *Listeria monocytogenes*^a
- Neonatal varicella^a
- *Pseudomonas* (ecthyma gangrenosum)^a
- Deficiency of interleukin-1 receptor antagonist (DIRA)
- Eosinophilic pustular folliculitis
- Erosive pustular dermatosis of the scalp
- Hyperimmunoglobulin E syndrome
- Langerhans' cell histiocytosis
- Neonatal Behçet disease
- Pustular eruption of myeloproliferative disorders (e.g., in Down syndrome)
- Pustular psoriasis
- Sweet syndrome

^aInfections.

BOX 10.2 CONDITIONS IN NEONATES WHERE BULLAE PREDOMINATE

COMMON CAUSES

- Bullous impetigo^a
- Sucking blisters

UNCOMMON CAUSES

- Staphylococcal scalded skin syndrome^a
- Epidermolysis bullosa

RARE CAUSES

- Group B streptococcal infection^a
- *Pseudomonas*^a
- Congenital syphilis^a
- Neonatal varicella^a
- Absent dermal ridge patterns, milia, and blisters of fingertips and soles
- Acrodermatitis enteropathica
- Bullous mastocytosis
- Bullous pemphigoid
- Chronic bullous dermatosis of childhood (linear IgA disease)
- Epidermolytic hyperkeratosis
- Maternal bullous disease
 - Pemphigus vulgaris
 - Herpes gestationis
 - Pemphigus foliaceus
- Membranous aplasia cutis congenita
- Toxic epidermal necrolysis

^aInfections.

TABLE
10.3

Differential diagnosis of vesiculopustular diseases – Uncommon and rare causes

Disease	Usual age of onset	Skin: morphology	Skin: usual distribution	Clinical: other	Diagnosis/findings
Acropustulosis of infancy	Birth or days to weeks	Vesicles and pustules	Hands and feet, occasional lesion elsewhere	Severe pruritus accompanying lesions which tend to come in crops	Clinical; skin biopsy: intraepidermal vesicle/pustule
Eosinophilic pustular folliculitis	Birth or days to weeks	Pustules, erythema	Mainly scalp and face; occasionally trunk, extremities	Pruritus; waxing and waning course with recurrent crops	Skin biopsy: dense perifollicular mixed infiltrate with eosinophils
Incontinentia pigmenti	Birth to days	Vesicles, hyperkeratosis in linear array	Most common on trunk, scalp, extremities	Extracutaneous involvement common but often not evident at birth. Mothers may have history of IP or other findings (e.g., missing teeth, areas of decreased hair growth)	Skin biopsy: eosinophilic spongiosis with dyskeratosis. Gene testing can also be used to establish diagnosis in atypical cases
Neonatal Behçet disease	First week of life	Small punched out vesicles, pustules, ulcerations and scarring	Perioral and oral mucous membranes, hands and feet, occasionally other sites	Maternal history of Behçet disease	Clinical findings and maternal history
Erosive pustular dermatosis of the scalp	Weeks to months	Crusting, pustules, scaly erythema	Scalp, superimposed on areas of alopecia, scarring from scalp injury	Severe scalp edema or necrosis of delivery; similar findings in Hay–Wells and Rapp–Hodgkin ectodermal dysplasias	Clinical findings and prior history of scalp injury or ectodermal dysplasia
Hyper-IgE syndrome	Days to months	Single or grouped pustules, vesicles, or crusting	Face, scalp, upper torso	Blood eosinophilia. Note: IgE levels often become elevated after neonatal period	Skin biopsy: intraepidermal vesicle with eosinophils or eosinophilic folliculitis. Gene testing for STAT-3 mutation
Lipoid proteinosis	Usually ≥1 year	Erythematous papulovesicular lesions resulting in atrophic scarring	Face, ears, extremities and occasionally trunk	Thickening of the skin, especially lips, perinasal skin, tongue; hoarseness	Skin biopsy shows thick hyalinized material with characteristic PAS-positive staining. Positive FH in some cases
Pustular psoriasis or deficiency of interleukin-1 receptor antagonist	First weeks or months of life	Pustules generalized, but especially palms, soles; may have underlying erythroderma	Generalized	Irritability, occasionally fever	Skin biopsy: epidermal microabscesses and acanthosis, parakeratosis, dilated capillaries
Pustular eruption of myelodysplasia in Down syndrome/neonatal eosinophilic pustulosis	First few days to months of life	Extensive pustules on erythematous base, often aggregating in areas of skin injury	Face most common site but can occur elsewhere	Very high WBC count: usually in setting of Down syndrome but can occur without obvious Down phenotype or with other causes of severe leukocytosis	Clinical and very high WBC. Skin biopsy: intraepidermal spongiosis with perivascular infiltrate of immature myeloid cells or eosinophils

perianal streptococcal disease.¹⁴ Blistering distal dactylitis (bullae on the volar tip of the digits usually due to Group A streptococcal infection) can rarely be caused by *Staph* in infants.¹⁵ Methicillin-sensitive and -resistant *Staphylococcus*, as well as herpes simplex infections can cause similar bullae; co-infection with *Staph* and HSV has been documented in a child.^{16,17} Infants with atopic dermatitis and staphylococcal superinfection usually present with crusting rather than intact pustules because of the tendency to scratch the primary lesion. Diagnosis and management are discussed in [Chapter 12](#).

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Staphylococcal scalded skin syndrome (SSSS) is an acute, potentially life-threatening disease caused by exotoxin-producing *S. aureus*, usually phage types 1, 2, or 3. Although epidemics as well as sporadic outbreaks of SSSS have been reported, including in newborn nurseries,¹⁸ it is still an uncommon to rare condition. A population-based study in Germany found an incidence of approximately 0.1 cases per million inhabitants per year (including all ages) with a bimodal

TABLE 10.4 Differential diagnosis of bullae, erosions, and ulcerations – Infectious causes

Disease	Usual age of onset	Skin: morphology	Skin: usual distribution	Clinical: other	Diagnosis/findings
Staphylococcal scalded skin syndrome	Few days to months or years. Years; rarely congenital	In neonate: widespread erythema, fragile bullae, erosions In older infants: macular erythema with accentuation of fold areas and scaling or crusting around mouth and nose more prominent	Generalized with periorificial accentuation	Neonates: irritability, lethargy, temperature instability Older infants: fever, irritability is variable but usually present	Biopsy: epidermal separation at granular cell layer. Cultures of skin, conjunctiva, throat, blood, urine or other sites demonstrate <i>S. aureus</i>
Group B streptococcal infection	At birth or first few days. Occasionally in older infants	Vesicles, bullae, erosions, honey-crusted lesions Older infants: occasionally blistering dactylitis	Any area	Pneumonia, bacteremia, meningitis	Gram stain: Gram-positive cocci in chains; bacterial culture
<i>Pseudomonas</i> infection	Days to years	Erythema, pustules, hemorrhagic bullae, necrotic ulcerations	Any area, but especially diaper, periorificial	In neonates: often history of surgery or other severe illness, e.g., necrotizing enterocolitis. In older infants usually immunocompromise Lack of prenatal care, organomegaly; bony lesions on X-ray, etc. Extreme prematurity or immunocompromised state	Skin or tissue Gram stain: Gram-negative rods; cultures of skin, blood Darkfield exam of skin; FA; syphilis serologies, skin biopsy
Congenital syphilis	Birth or first few days	Bullae or erosions	Especially hands, feet, and periorificial		Skin biopsy: septate hyphae; tissue fungal culture
<i>Aspergillus</i> infection	Few days to weeks or months to years	Pustules often clustered, rapidly evolve to ulcers	Any area but more common in areas occluded by tape, armboard, etc.		
Zygomycosis/trichosporosis	Days to weeks	Generalized peeling and skin breakdown or cellulitis evolving into necrotic ulcer	Any area	Extreme prematurity or immunocompromised state	Skin biopsy and tissue fungal culture
Intrauterine herpes simplex infection	Birth	Vesicles, pustules, widespread erosions, scars, areas of missing skin	Any site	Low-birthweight; microcephaly; chorioretinitis; history of maternal fever, discordance of HSV infection in mother and father Atopic dermatitis	Tzanck; FA or immunoperoxidase slide test, PCR, viral culture Tzanck, FA, viral culture
Eczema	Months to years	Discrete circular 1–2 millimeter erosions in a 'honeycomb' pattern	Any site		
Fetal varicella infection	At birth	Scarring, limb hypoplasia, erosions	Any site but often extremity	Maternal chickenpox first trimester	
Varicella	Months to years	Vesicles and erosions on red base; bullae rare – only in immunocompromised neonates or infants	Generalized	Unimmunized children at higher risk	Tzanck, FA, viral culture

TABLE
10.5

Differential diagnosis of bullae, erosions, and ulcerations – Transient skin lesions

Disease	Usual age of onset	Skin: morphology	Skin: usual distribution	Clinical: other	Diagnosis/findings
Sucking blisters	At birth	Flaccid bulla or linear erosion – occasionally two symmetric lesions	Fingers, wrists, occasionally foot	Sucks on affected areas	Clinical
Perinatal trauma/iatrogenic injury	At birth or neonatal period	Erosions, ulcerations	Depends on cause of trauma	Perinatal history of monitoring, prolonged labor and/or vacuum or forceps delivery; other monitoring. More common in premature infants	History and clinical findings
Insect bite hypersensitivity	Months to years	Tense vesicles and bullae usually on red base with or without urticarial papules: often grouped in 'breakfast, lunch, dinner' pattern	Ankles, anterior shin, waistline most common but can be elsewhere	Exposure to fleas or other insects not always known, but this does not exclude diagnosis	Clinical findings; skin biopsy if extensive or atypical

BOX 10.3 CONDITIONS IN NEONATES WHERE EROSIONS OR ULCERATIONS PREDOMINATE

COMMON CAUSES

- Skin changes due to perinatal/neonatal trauma
 - Diaper erosions
 - Scalp electrode injury
 - Skin trauma due to adhesives, etc.
- Sucking blisters

UNCOMMON CAUSES

- Herpes simplex, especially congenital^a
- Staphylococcal scalded skin syndrome^a
- Aplasia cutis congenita
- Epidermolysis bullosa
- Infantile hemangiomas presenting with ulcerations

RARE CAUSES

- *Aspergillus*^a
- Congenital syphilis^a
- Group B streptococcus^a
- Intrauterine herpes simplex^a
- Intrauterine varicella^a
- Noma neonatorum^a
- *Pseudomonas* (ecthyma gangrenosum)^a

- Zygomycosis/trichosporosis^a
- Acrodermatitis enteropathica
- Bullous congenital ichthyosiform erythroderma
- Congenital deficiency of protein C, S, or fibrinogen
- Congenital erosive and vesicular dermatosis
- Erosive pustular dermatosis of the scalp
- Focal dermal hypoplasia
- Giant congenital melanocytic nevi
- Hemangiomas and vascular malformations
- Intrauterine epidermal necrosis
- Linear porokeratosis
- Methylmalonic acidemia and other metabolic disorders
- Neonatal lupus erythematosus with intrauterine onset
- Perinatal gangrene of the buttock
- Porphyrrias
 - Transient porphyria
 - Erythropoietic porphyria
- Pyoderma gangrenosum
- Rapidly involuting congenital hemangioma (RICH)
- Restrictive dermopathy
- Toxic epidermal necrolysis
- Vascular malformations (e.g., CMTC, occasionally others)

^aInfections.

distribution of ages: young children and older adults.¹⁹ In a group of neonates and infants with erythroderma, SSSS was the etiology of their skin findings in only 7%.²⁰ Only a few cases of congenital SSSS have been reported; the vast majority of infants present between 3 and 7 days of age or older, with an abrupt onset of cutaneous erythema, tenderness, and widespread areas of skin fragility, superficial blistering, and/or erosions.^{21–24} Erythema often begins on the face, especially around the mouth. In newborns, flaccid blisters usually appear within 24–48 h and quickly erode, producing areas of superficially denuded skin. These erosions are particularly prominent in areas of mechanical stress, such as the shoulders, buttocks, body folds, feet, and hands. When firmly rubbed, the skin is easily separated from the underlying epidermis (Nikolsky's sign). A milder, but more common form of SSSS, characterized by erythema, tiny

erosions or pustules, with or without a scarlatiniform rash is often seen in older infants and children. Periorificial accentuation with scale or crusting is a common feature of both forms (Fig. 10.4).

Systemic signs such as temperature instability, irritability, and/or lethargy are common in neonates whereas infants are nearly always febrile. Perioral or periorcular edema and mucopurulent conjunctivitis are sometimes present. Although the primary site of *S. aureus* infection is usually not the skin, occasionally a primary skin infection, such as an abscess, purulent umbilicus, or localized area of impetigo, may be the source of disease.¹¹

Diagnosis is made by skin biopsy, which demonstrates a cleavage plane in the upper epidermis with acantholytic cells and minimal dermal inflammation. To speed diagnosis, a snip

TABLE 10.6 Differential diagnosis of bullae, erosions, and ulcerations – Uncommon and rare causes

Disease	Usual age of onset	Skin: morphology	Skin: usual distribution	Clinical: other	Diagnosis/findings
Epidermolysis bullosa	At birth or first few days	Bullae and skin fragility; depending on type: mucosal erosions, aplasia cutis of anterior leg, milia, nail dystrophy, etc.	Depends on type: accentuated in areas of trauma such as extremities, hands, feet	Pain, irritability and difficulty feeding. Occasionally cornel, respiratory tract, or gastrointestinal (pyloric atresia); anemia	Skin biopsy of blister <24 h or induced with friction; specific type diagnosed with electron microscopy or immunofluorescent mapping
Bullous mastocytosis	Birth or weeks to months	Localized form: infiltrated nodular area with intermittent superimposed wheal or bullae; generalized form: blistering usually superimposed on infiltrated skin	Any site: often on torso	Variably present: hives, flushing, irritability, sudden pallor, diarrhea	Biopsy demonstrating increased mast cells in dermis
Maternal bullous disease	Birth	Depends on type of maternal disease: tense or flaccid bullae or erosions	Usually generalized	Maternal history of blistering disease but occasionally inactive at time of pregnancy	Maternal history; skin biopsy and direct immunofluorescence with results depending on maternal type
Chronic bullous dermatosis of childhood	Rarely in neonatal period; usually onset later in infancy or childhood	Tense blisters often form rosette or sausage shapes	Generalized but often concentrated on buttocks, thighs; usually spares mucosa	Usually absent	Skin biopsy: subepidermal bullae; direct immunofluorescence: linear pattern IgA DEJ
Bullous pemphigoid	≥2 months of age	Tense blisters	Often accentuated on hands and feet but may be generalized	Usually absent	Skin biopsy: subepidermal bullae; direct immunofluorescence: linear pattern IgA DEJ
Toxic epidermal necrolysis	Rare in neonates except in rare cases of intrauterine graft-vs-host disease. Most cases have onset at age ≥6 weeks	Erythema, erosions, bullae and cutaneous tenderness usually with mucous membrane involvement	Generalized, evolving rapidly over hours to days	In neonates and very young infants: may be associated with Gram-negative sepsis or due to IU GVHD. In older infants usually medication-induced	Superepidermal blister with widespread epidermal necrosis (usually full-thickness)
Intrauterine epidermal necrosis	Birth	Widespread erosions and ulceration without vesicles or pustules	Generalized, spares mucous membranes	Prematurity and rapid mortality	Skin biopsy: epidermal necrosis and calcification of pilosebaceous follicles
Congenital erosive and vesicular dermatosis	Birth	Erosions, vesicles, crusts, erythematous areas	Generalized, usually sparing face, palms, soles	Prematurity, variably: collodion membrane, transparent skin, reticulated vascular pattern	Clinical diagnosis, often retrospective. Skin biopsy: neutrophilic infiltrate; exclusion of other etiologies of erosions, vesicles
Pyoderma gangrenosum	Rare cases in neonates; rare in infants but can occur	Sharply demarcated ulcerations with undermined borders	Any site, but usually groin, buttock in infants	Many associations, including immunodeficiency disorders and inflammatory bowel disease	Clinical, exclusion of other etiologies; skin biopsy with neutrophilic infiltration without vasculitis, infection, etc.
Noma neonatorum	Days to weeks	Deep ulcerations, with bone loss, mutilation in some cases	Nose, lips, intraoral, anus, genitalia	Some cases due to <i>Pseudomonas</i> . Others due to malnutrition, immunodeficiency	Clinical; exclusion of other etiologies, especially infection

Acrodermatitis enteropathica/ 'Acrodermatitis dysmetabolica'	Weeks to months	Sharply demarcated crusted plaques; occasionally vesicles, bullae, erosions	Periorificial, i.e., mouth, nose, eyes, genitalia as well as neck folds, hands, and feet	Premature, breast-fed infants with low maternal milk zinc; prolonged parenteral hyperalimentation; can see similar presentation with cystic fibrosis and other metabolic diseases	Low serum zinc levels (usually <50 µg/dL)
Methylmalonic acidemia	Days to weeks	Erosive erythema	Periorificial accentuation	Lethargy, hypotonia, neutropenia, low platelets	Characteristic abnormalities of plasma amino acids
Restrictive dermopathy	Birth	Rigid tense skin with erosions, linear ulcerations	Generalized skin abnormalities	Joint contractures, micrognathia, natal teeth	Clinical; distinguish from Neu-Laxova syndrome
Infantile hemangiomas	Birth or first few days, weeks or months	Ulceration without preceding primary vesicles or bullae; usually with surrounding area of bright red erythema	Any site, but most often perianal, perineal, gluteal cleft, neck fold, or perioral	Associated hemangioma may or may not be obvious at onset of the ulceration	Clinical or skin biopsy showing proliferation of Glut-1 positive blood vessels
Aplasia cutis congenita	Birth	'Bullous' form: sharply demarcated with overlying membrane; other types with raw, full-thickness defect skin	Scalp or face most common; other sites depending on etiology	Depends on etiology: CNS defects, trisomy 13, limb-reduction abnormalities	Usually clinical; imaging studies to evaluate underlying bone, CNS
Linear porokeratosis or porokeratotic adnexal ostial nevus	Birth	Linear erosions initially; over time more scaly areas evident; follows the lines of Blaschko	Extremities, torso, any skin site possible	Eventual risk of squamous CA	Skin biopsy: cornoid lamella – may not be evident in newborn period
Erosions overlying giant nevi	Birth, first few days	Erosions, ulcerations	Superimposed on giant nevi, particularly over back	In some cases, neurocutaneous melanosis	Clinical and biopsy to exclude melanoma if persistent ulcerations or other unusual features present
Focal dermal hypoplasia	Birth	Occasional blisters, but more often hypoplasia, aplasia of skin	Linear and whorled pattern, often arms, legs, scalp	Skeletal, eye, and CNS abnormalities to varying degree	Clinical; family history; skin biopsy
Absent dermal ridges and congenital milia syndrome	Birth	Multiple bullae	Fingers, soles of feet	Absent dermal ridge patterns, multiple milia	Clinical; family history (autosomal dominant)
Porphyria	Days to weeks or months	Blistering and erosions leaving shallow scars or milia in sites exposed to sunlight, phototherapy lights, or in severe cases visible light only		Transient form usually due to hemolytic anemia with transient elevated porphyrins. Rarer form is congenital erythropoietic porphyria (CEP)	Transient: elevated plasma porphyrins. CEP: pink urine; elevated urine, fecal and plasma porphyrins
Perinatal gangrene of the buttock	Days	Sudden onset erythema, cyanosis, and gangrenous ulcerations	Buttocks	Umbilical artery catheterization usual associated finding	Clinical
Neonatal purpura fulminans	Days	Initially purpura or cellulitis-like areas evolving to necrotic bullae or ulcers	Buttocks, extremities, trunk and scalp most common sites	Other sites of DIC	Prolonged PT, PTT, low fibrinogen, elevated FDPs; low protein C or S levels



Figure 10.1 Papules, pustules, and crusted erosions in a 9-month-old infant with *S. aureus* infection. Note evolution of primary lesions (papules and pustules) to secondary crusted erosions.



Figure 10.2 Numerous pustules due to *S. aureus* infection with follicular accentuation.

biopsy of exfoliating portions of the skin can be sent for frozen section. The differential diagnosis includes toxic epidermal necrolysis, epidermolysis bullosa, boric acid poisoning, and certain metabolic disorders such as methylmalonic acidemia.^{25,26} The management of SSSS is discussed in [Chapter 12](#).



Figure 10.3 Staphylococcal impetigo in this 9-month-old infant with features of exotoxin-producing *S. aureus*, including collarettes of scale, larger areas involvement and shellac-like superficial scale.



Figure 10.4 Staphylococcal scalded skin syndrome in a young infant. Note periorificial accentuation and fragile vesicles overlying erythema on neck.

STREPTOCOCCAL INFECTION

Several epidemics of group A streptococcus (GAS) have been reported in the newborn period. Although most infants present with omphalitis or a moist umbilical cord stump, in rare cases isolated pustules may be the presenting sign of GAS infection. GAS can also cause a form of intertrigo in infancy.^{27–29} Generalized sepsis, cellulitis, meningitis, and pneumonia are occasionally seen.^{30,31} Because neonatal group A streptococcal infection can result in an invasive infection, parenteral antibiotics should be considered, and infants observed closely for signs of systemic

illness. Although bacterial cultures are the 'gold standard' for diagnosis, rapid antigen testing for GAS can be used while awaiting culture.

In older infants, clinical presentations of localized cutaneous GAS infection include impetigo, streptococcal intertrigo, perianal streptococcal dermatitis, blistering dactylitis and atopic dermatitis with secondary streptococcal infection. GAS impetigo can be difficult to distinguish from that caused by *S. aureus*: both have crusting and erosions and occasional pustules. In addition, infants with GAS skin infections may be more irritable and may be febrile, a finding less common in *S. aureus* impetigo. Infants with streptococcal intertrigo, have moist eroded areas in the folds of the neck, axilla, groin, or perianal area that can be mistaken for candidal infection.^{27–29} In young children with blistering distal dactylitis, a large vesicle or bulla develops on the volar aspect of tips of fingers or toes.³² In infants with atopic dermatitis, GAS causes crusting and pustules that may be deep-seated and may involve the palms and soles – a feature less likely to be due to *S. aureus* alone; coinfection with staphylococcus can occur (Fig. 10.5).^{33,34}

Infection with group B β -hemolytic streptococci (GBS) is one of the most common causes of neonatal sepsis, but skin lesions resulting from GBS infection are very rare. In a few cases cellulitis, vesicles, bullae, erosions, and honey-crusted lesions resembling GAS impetigo have been described^{11,35–38} either at the time of birth or later in the neonatal period.³⁶ Many areas of the body, including the scalp, face, submandibular area, torso, and extremities, can be affected, with lesion size varying from a few millimeters to several centimeters.³⁷ Other manifestations of group B streptococcal disease (including bacteremia, pneumonia, and meningitis) should be sought. GBS is also an occasional cause of blistering dactylitis or impetigo.

LISTERIA INFECTION

Listeria monocytogenes is an uncommon cause of a rare form of sepsis in the newborn period, typically acquired via vertical transmission from an affected mother. Epidemics and sporadic cases due to inadequately pasteurized and more rarely pasteurized dairy products have been reported.^{39–41} Skin disease, when it occurs, is associated with an early-onset form of infection which is present at birth or develops in the first few days of life (so-called granulomatosis infantiseptica). The rash, which is usually present at birth, consists of discrete but widespread pustules and petechiae over the trunk and extremities. In less severely affected infants, erythematous macules may progress to pustules with an erythematous halo. Salmon-colored papules concentrated on the trunk have also been described.^{39,41} Typically, maternal fever, fetal tachycardia, and meconium staining of amniotic fluid are present before delivery, and premature delivery is common. Affected infants are usually gravely ill, with respiratory distress, meningitis, and other signs of sepsis.

The differential diagnosis includes several other infections, including congenital candidiasis, intrauterine herpes infection, and *Haemophilus influenzae* infection. Further details of diagnosis and management are discussed in Chapter 12.

HAEMOPHILUS INFLUENZAE INFECTION

Haemophilus influenzae is a very rare cause of neonatal skin disease. Findings have included vesicles, pustules, crusted areas, and abscesses.^{42,43} Halal and colleagues provided the best descriptions of skin lesions in an infant with discrete vesicles

on an erythematous base, as well as several 2–3 mm crusted areas, present at birth. Gram stains and culture from skin lesions confirmed the presence of *H. influenzae* type B, but cultures from other sites were negative.⁴³ Onset of symptoms is at birth or in the first few days of life.

If *H. influenzae* is suspected, diagnostic evaluation should include Gram stain and culture of skin lesions, and cultures of the infant's blood, urine, cerebrospinal fluid (CSF), and nasopharynx. Cultures of the placenta (if available) and of the maternal cervix and lochia should also be performed. The differential diagnosis includes other infections. A Gram stain demonstrating pleomorphic Gram-negative bacilli is strong evidence for *H. influenzae* infection. Treatment is discussed in Chapter 12.

PSEUDOMONAS INFECTION

Pseudomonas aeruginosa in newborns nearly always occurs after 5 days of life, most commonly in infants weighing less than 1500 g at birth. Risk factors include feeding intolerance, parenteral nutrition, prolonged intravenous antibiotics, and necrotizing enterocolitis.⁴⁴ Skin lesions are usually a result of septicemia and hematogenous spread of infection to the skin. However, in older infants, ulcerative skin lesions of *Pseudomonas* have been reported in the diaper area and in previously healthy young infants in the absence of documented blood-borne infection or immunodeficiency.^{45–47} Some of these patients are ultimately diagnosed with neutropenia or immunodeficiency. Thus, apparently healthy older infants with ecthyma gangrenosum should be thoroughly evaluated for predisposing conditions.⁴⁸ Older infants immunocompromised from cancer treatment or transplant are also at risk for pseudomonas infection.

The skin lesions of *Pseudomonas* infection are known as 'ecthyma gangrenosum'.⁴⁹ They typically evolve from areas of erythema to hemorrhagic bullae or pustules. The pus may be green, caused by a dye produced by the bacteria. Lesions rapidly erode, becoming punched-out necrotic ulcerations with an indurated base.⁵⁰

In septicemic forms, the affected neonates or immunocompromised infants are usually gravely ill; prompt diagnosis and rapid institution of treatments are necessary to prevent death from overwhelming sepsis.⁴⁹ Gram staining of fluid from a pustule or bulla will reveal Gram-negative rods. If lesions are eroded, biopsy and tissue Gram staining should be performed to expedite diagnosis. Cultures of both the skin and blood will confirm the diagnosis. Treatment of suspected infection must take into account the local patterns of antibiotic resistance and is discussed in Chapter 12.

CONGENITAL SYPHILIS

Congenital syphilis is a very rare neonatal infection in the USA and most often occurs in the setting of inadequate prenatal care.⁵¹ Rarer still is presentation with blistering or ulcerations. These findings occur almost exclusively in early-onset disease and are present in approximately 3% of cases, usually at the time of birth.^{52,53} Bullae are most often located on the palms, soles, knees, or abdomen, superimposed on dusky, hemorrhagic, or erythematous skin.⁵⁴ Moist areas of eroded skin may also occur around the mouth, nose, and anogenital area.⁵¹ Typical skin rashes in congenital syphilis are seen more often in preterm than term infants.⁵⁵ Generalized erythema multiforme-like lesions with vesicular centers have also been reported in an infant with congenital syphilis.⁵⁶



Figure 10.5 Group A streptococcal impetigo. In contrast to *S. aureus* infection, palms and soles are more common sites of infection. Overlapping features of both bacteria make it virtually impossible to distinguish these without confirmatory bacterial culture.

Blistering congenital syphilis must be differentiated from other disorders causing blistering on the palms and soles, including congenital candidiasis, acropustulosis of infancy, scabies, and epidermolysis bullosa. The clinical findings, as well as serologies, potassium hydroxide (KOH) preparation, and skin biopsy when necessary, help in this differentiation. The details of the evaluation and therapy of congenital syphilis are discussed in [Chapter 12](#).

Fungal infections (see Chapter 14)

Nosocomially acquired fungemia is an increasingly common cause of morbidity and mortality in neonates, particularly very low-birthweight, and otherwise immunocompromised infants. Most cases are due to *Candida* spp., but infections from *Aspergillus*, *Trichosporon*, and other fungi have been reported.

CANDIDA

Candida albicans infection is very common in infants but presentation with a primarily vesiculopustular eruption is much more common in neonates and is the focus of this discussion. Several candidal species can cause infections in neonates. Depending on the case series, *C. albicans*, *C. parapsilosis*, and to a lesser degree *C. tropicalis* are the most frequent isolates.^{57,58}

Congenital candidiasis and invasive candidal 'dermatitis'

The cutaneous signs associated with candidal infections have been most clearly delineated for *Candida albicans* infection. *Congenital candidiasis*, a rare condition, is due to exposure to *C. albicans* in utero. It typically presents at birth or within the first week of life as a widespread eruption. Risk factors include a foreign body in the uterus or cervix (such as a retained intrauterine device or cervical suture), premature delivery, and a maternal history of vaginal candidiasis.^{59,60} Several types of skin lesions may be present, including diffuse erythema, erythematous papules, vesicopustules, and fine scaling.⁶¹ Typically, a fine erythematous papular eruption involving the face and upper body develops first, evolving over time into a more widespread pustular and scaly eruption. In milder cases, sparse papules and incipient pustules are scattered over the upper chest, back, and extremities. Virtually any part of the skin may be involved; unlike many pustular eruptions (such as erythema toxicum and miliaria), the palms and soles are often involved ([Fig. 10.6](#)).⁶⁰ Nail dystrophy and oral thrush are occasionally present.

The terms 'invasive fungal dermatitis' or 'candida-like dermatitis' are used to describe a more severe type of candidal skin infection seen in very low-birthweight infants. This form of infection may not be present at birth but can typically be noticed within the first 2 weeks of life, occasionally later. Diffuse erythema and scaling with superficial erosions resembling a first-degree burn have been reported and may evolve into full-thickness skin infection and necrosis. This finding in very low-birthweight infants is associated with high rates of positive blood cultures, as well as pulmonary and other sites of infection.^{57,62} Skin abscesses have also been reported as an early finding of systemic candidiasis.⁶³ Diagnosis can often be confirmed with potassium hydroxide (KOH) preparation and/or culture from involved skin. Organisms are often present in large numbers even in cases where pustules are relatively sparse, but



Figure 10.6 Congenital candidiasis in a 5-day-old infant. Scaling, erythema and tiny pustules are the most common features. Palm and sole involvement is common. (Courtesy of Vinod Bansal, MD.)

if necessary, skin biopsy can also help confirm the diagnosis. *Candida* may also be present in the gastric aspirate.

Differential diagnosis includes *Listeria* and intrauterine herpes simplex infections, erythema toxicum neonatorum, pustular miliaria rubra, and neonatal pustular melanosis.

Treatment depends on the gestational age and weight: premature infants weighing <1500 g have a much greater risk of disseminated candidiasis and need further investigations, such as blood, spinal fluid, and urine cultures, and immediate institution of systemic therapy (see [Chapter 14](#)). Infants with a higher birthweight and gestational age, without evidence of disseminated disease must be observed closely because on rare occasions, systemic infection, with respiratory distress or other organ involvement, may develop;⁶⁴ however, topical therapy with an imidazole cream may be curative.

Neonatal candidiasis is the term used for infants that present with *Candida* infection after 1 week of life and are infected due to peripartum or postnatal exposure,⁶⁵ and can occur in both term and preterm infants. Colonization with *C. albicans* is very common, occurring in approximately one-quarter of infants >1500 g birthweight, and nearly one-third of those colonized develop mucocutaneous disease.⁶⁶ The most common sites of involvement are the diaper area and the oral mucous membranes, but other intertriginous areas or areas which have had tape or occlusion may be affected, e.g., facial eruption if the infant has been intubated.¹¹ The most typical presentation is beefy red scaly patches with satellite papules at the periphery. Pustules at the periphery of lesions can be seen, but are less common and can be very subtle. Topical therapy with an imidazole cream or nystatin ointment is usually sufficient because dissemination does not develop in immunocompetent infants, but closer monitoring is mandated for very low-birthweight infants with evidence of postnatally acquired candidiasis.⁵⁷

Candidal infection in older infants

In immunocompetent older infants outside the neonatal period, cutaneous candidal infection is usually limited to the diaper area, where vesicles and pustules may be located on the margin of a red confluent plaque ([Fig. 10.7](#)). *Candida* colonizes the diaper area more heavily in infants with diaper dermatitis even



Figure 10.7 Acquired *Candida albicans* diaper rash in a 3-week-old infant. Peripheral tiny pustules are evident.

without overt infection.⁶⁷ Differential diagnosis of the pustules includes bacterial infections with *staphylococcus* or *streptococcus* (see Chapter 14 for further discussion). In the immunocompromised host, clinicians should maintain a high index of suspicion for invasive disease (see also Chapter 18).^{58,68}

ASPERGILLUS INFECTION

Primary cutaneous aspergillosis has been reported in neonates, most of whom were very premature, but it can also occur at any age including infancy, most often in the setting of severe immunocompromise. *Aspergillus fumigatus*, *A. niger*, and *A. flavus* can all cause skin disease. The usual age at diagnosis in neonates typically ranges from 1 week to 1 month.⁶⁹ Predisposing factors in addition to prematurity include prior treatment with systemic antibiotics or, less commonly, use of systemic corticosteroids.

In both primary and secondary skin disease, a variety of skin lesions have been reported, including pustules and ulcerations, often superimposed on indurated plaques, but the most common of these is skin ulceration, which may feature a central necrotic-appearing eschar, with punched-out ulcers at the periphery.⁷⁰

Skin lesions are usually the result of primary cutaneous disease, where the skin is the initial or only site of infection, often preceded by skin maceration or injury, e.g., abrasions from adhesive tape. Hospital renovations and construction are risk factors in some cases.⁷¹ Secondary cutaneous disease occurs after hematogenous spread to the skin from the primary site of infection, most commonly the lungs. In secondary disease, lesions may be more extensive; they are most commonly located on the perineum and buttock.^{69,72,73} A third form of aspergillosis reported in the immunocompromised is infection of a cavity such as a sinus, with contiguous mucocutaneous spread, similar to that seen in other fungal infections like mucormycosis.

Skin biopsies, which demonstrate dermal inflammation and broad anastomosing septate hyphae on special stains, are usually necessary for diagnosis, with culture for confirmation. (Management is discussed in Chapter 14.) The prognosis is guarded, both because of possible systemic aspergillosis and because of other diseases associated with prematurity.⁷²

TRICHOSPOROSIS AND ZYGOMYCOSIS

More than a dozen cases of *Trichosporon* infection (see Chapter 14) have been reported in neonates, most of whom were very low-birthweight due to prematurity. Infection can be associated with generalized skin breakdown, peeling, and oozing without vesicles or pustules, as well as necrotic eschar formation.^{74,75} Mucormycosis has been reported more frequently, again nearly all in very low-birthweight or otherwise immunosuppressed infants. The age at diagnosis varied from 4 to 33 days. Damage to the skin from adhesive tape and/or invasive catheters is felt to be an important risk factor. This, combined with prematurity, broad-spectrum antibiotics, and in some, the systemic use of corticosteroids, is a factor conducive to these opportunistic pathogens. Mucormycosis in this setting typically presents as vesicles, pustules, or cellulitis, or an area of skin discoloration, which evolves into a black necrotic ulcer with surrounding erythema. Skin biopsy is usually needed for diagnosis.^{76,77} In older immunosuppressed infants, there is a similar clinical picture.⁷⁸ Both types of infection have a poor prognosis but treatment

with amphotericin B (with or without surgical debridement) has been successful in some cases.

Viral infections (see Chapter 13)

HERPES SIMPLEX INFECTION

Herpes simplex (HSV) infection is one of the most feared causes of blisters and pustules in the newborn. Subtle or inconspicuous skin lesions may herald the onset of infection, and the failure to promptly recognize and treat neonatal HSV infection can worsen the prognosis of this potentially devastating disease. Skin lesions are present in both intrauterine and neonatal herpes simplex infection, and although there is considerable overlap, the time of onset and many of the clinical features of the skin disease differ.

In *intrauterine HSV infection*, skin lesions are usually present at the time of birth, or develop within 24–48 h in 90% of affected infants. In addition to the characteristic vesicular eruption, widespread bullae and erosions resembling epidermolysis bullosa,^{79,80} absence of skin on the scalp (resembling aplasia cutis congenita), polycyclic plaques with erosions, scars on the scalp, face, trunk, or extremities, and absence of nail plates have been reported.^{81,82} Affected infants are often premature, weighing less than 2500 g, and most have other manifestations of TORCH infections e.g. microcephaly and chorioretinitis. Some have limb and bone abnormalities.⁸²

In contrast, *neonatal HSV infection* is acquired perinatally and presents with three characteristic patterns: mucocutaneous disease (limited to the skin, eyes, or mouth, or SEM); disseminated disease (with evidence of visceral organ involvement, including liver, lungs, or disseminated intravascular coagulation); and central nervous system disease (where CSF or brain abnormalities are present in the absence of other visceral disease). Skin lesions may occur in all three types.^{83,84}

Skin disease is the most characteristic finding in neonatal HSV infection, but it often lags behind other symptoms in onset and is noted in less than half of infants with disseminated and CNS disease at presentation. Feeding problems and lethargy are the most common presenting complaints.^{85,86} Other signs of infection in neonates include lethargy, temperature instability, jaundice, coagulopathy, hepatitis, respiratory distress and neurologic deterioration.^{86,87} The average age at onset of symptoms is 6–8 days but the average age at diagnosis is 11–13 days, in part due to the lack of specific symptoms or characteristic skin lesions early in the disease course. Of infants with neonatal HSV infection, 17–39% never develop vesicles.⁸⁸ Conversely, most infants will develop vesicles at some point in the course of disease. These evolve over time into pustules, crusts, or erosions. Another important form of presentation is a poorly healing fetal scalp monitor site. Although grouped vesicles on an erythematous base are a hallmark of herpetic infection (Fig. 10.8), neonatal herpes lesions frequently lack such grouping, and in some cases a widespread vesicular exanthem or zoster-like blistering localized to one or two dermatomes may occur. Oral ulcerations are present in nearly one-third of cases.⁸⁹ Neonatal HSV can recur, more commonly with HSV-2 infection than HSV-1. Vesicles usually develop at the same site as the initial eruption.⁹⁰

A maternal history of primary herpes simplex infection, genital ulcerations during pregnancy (even if not diagnosed as HSV), and history of discordant infection with paternal but



Figure 10.8 Neonatal herpes simplex infection in a 13-day-old infant presenting as grouped pustules on an erythematous base. (Courtesy of Jeff Lindenberg, MD.)

not maternal history of genital HSV are all risk factors for infection. However, the majority of cases occur in women who are either asymptomatic or whose symptoms go unrecognized.⁹¹ Both intrauterine and neonatal herpes simplex infection can occur even when primary HSV infection is diagnosed during pregnancy and the mother is treated with prophylactic acyclovir, although vertical transmission may be reduced by prophylaxis.^{84,92}

If skin lesions suggest herpes infection, prompt diagnosis and institution of treatment is imperative. Skin scrapings of the blister base for Tzanck preparation are helpful in experienced hands, but direct immunofluorescent stains are more specific for rapid detection. Polymerase chain reaction (PCR) is another way to obtain fast preliminary diagnosis of HSV infection in skin, mucosa and CSF samples, and to assess treatment response.⁹² False-positive immunofluorescent studies have occasionally been reported.⁹³ Viral cultures remain the gold standard of diagnosis, and cultures of the skin, conjunctiva, throat, cerebrospinal fluid, and urine should be obtained.⁸⁹

The differential diagnosis of herpetic skin lesions depends on the specific clinical presentation and is summarized in [Table 10.5](#). The rarity of neonatal HSV infection in the USA was demonstrated in a study by Caviness and colleagues,⁸⁷ at the Texas Children's Hospital, the largest children's hospital in the USA: in a 14-year period, only 40 cases were identified, fewer than three per year. When neonates with HSV infection were compared with HSV-negative controls, infected neonates had the following associated factors: maternal primary HSV infection, maternal fever, vaginal delivery, prematurity, postnatal HSV contact, vesicular rash, hypothermia, lethargy, seizures, severe respiratory distress, hepatosplenomegaly, thrombocytopenia, elevated hepatic enzymes, and cerebrospinal fluid (CSF) pleocytosis and proteinosis.

This study serves to further emphasize that many other diseases share features with neonatal HSV. Vesicles and pustules per se are not specific or sensitive for diagnosing neonatal HSV. Moreover, there are some clinical presentations that are *unlikely to represent herpes simplex infection*. In particular, a vigorous, term infant with a widespread pustular eruption at the time of delivery or within a few hours thereafter is unlikely to have herpes simplex infection. This time course – if due to HSV

– would be due to intrauterine infection, which is typically associated with findings of TORCH infection. A premature infant with a widespread vesiculopustular eruption involving the palms and soles could have herpes infection, but is more likely to have congenital candidiasis. Although a high index of suspicion for herpes infection is appropriate, fear of neonatal HSV should not preclude a rational and systematic approach to differential diagnosis. The management of the infant presumed to have herpes simplex infection includes strict isolation and prompt institution of intravenous antiviral therapy⁸⁹ while awaiting cultures, and is discussed in more detail in [Chapter 13](#).

Infantile HSV infection

Most primary HSV infections in older infants and children are asymptomatic. The most common clinical syndrome is herpes gingivostomatitis: painful vesicles on the gingivae, oral mucosa and tongue. Extraoral vesicles can also develop anywhere but are especially common in the perioral region. Children with dense intraoral lesions are often quite symptomatic, have difficulty eating and drinking, and sometimes require hospitalization for rehydration and pain control.⁹⁴ Differential diagnosis includes viral enanthems, particularly enteroviral, and aphthous ulcers; the latter are rare in young infants. Other clinical manifestations of HSV in infants include herpetic whitlow and eczema herpeticum in infants with atopic dermatitis, which presents not with vesicles but with discrete erosions. See [Chapter 13](#) for further details regarding diagnosis and management.

VARICELLA

Cutaneous stigmata of varicella infection may occur in the newborn period as a result of early intrauterine infection, also referred to as the 'fetal varicella syndrome,' 'congenital varicella,' and 'varicella embryopathy.' Varicella can also occur as a result of intrauterine exposure just prior to delivery. This condition, which should more properly be called 'neonatal varicella,' is often referred to in the literature as 'congenital varicella.'

The fetal varicella syndrome may occur as a result of primary varicella infection in the mother, almost always during the first trimester of pregnancy.⁹³ Cutaneous features include dermatomal scarring and occasional skin ulcerations, but blisters and pustules are not usually present in the neonatal period.^{93,95,96}

Primary varicella in the neonatal period occurs in one-quarter of infants exposed to maternal varicella during the last 3 weeks of pregnancy, and can be especially severe if exposure occurs between 7 days before and 2 days after delivery.^{97,98} Onset is usually at 5–10 days of age. When maternal infection occurs between 1 and 3 weeks before delivery, partial transplacental immunity results in earlier onset of infection and milder disease.

The skin lesions in neonatal varicella begin as vesicles superimposed on an erythematous base, gradually becoming cloudy and then crusted. The clinical pattern often resembles that seen in immunocompromised hosts. Lesions may be extremely numerous, widespread, and monomorphic, with all lesions occurring at the same stage of development instead of varying. They may also be hemorrhagic and enlarge into bullae.

The most life-threatening complication of neonatal varicella is pneumonia. The diagnosis is usually obvious because of the maternal history. A positive Tzanck preparation and viral cultures are confirmatory. Management is discussed in [Chapter 13](#).

Young infants can develop primary varicella postnatally from community exposure. The characteristic rash begins as

itchy red macules on the scalp, face or trunk that evolve into vesicles on an erythematous base that then crust.⁹⁹

Herpes zoster in healthy children is uncommon. In the newborn period, it almost invariably results from exposure to varicella in utero, including later in pregnancy.^{100–102} HZ can occur later in infancy following primary varicella in utero or infection early in infancy. Wild-type virus can rarely cause HZ even in children who have been vaccinated and have not had a clinically evident infection.¹⁰³ Like older children and adults, infants with HZ develop vesicles in a dermatome of a sensory nerve that spread and coalesce. Multiple dermatomes can be involved. Associated symptoms like fever, adenopathy and irritability can accompany the rash. HZ can recur, usually in the same dermatome as the initial episode. Other causes of localized vesicles in infants include HSV infection, bullous impetigo, vesicular insect bite reactions and contact dermatitis.¹⁰⁴

Cytomegalovirus (CMV) is a relatively common cause of intrauterine and perinatal infection, but presentations with vesicles, bullae or ulcerations are quite rare.^{105–107} In one case report, a premature and growth-retarded infant with hepatitis had two vesicles on the forehead, and blister fluid, as well as saliva and urine, produced a cytopathic effect characteristic of CMV in cell culture.¹⁰⁵ Another term infant who was immunocompetent presented at 3 weeks of age with CMV hepatitis and vesicles and bullae on the face, chest and buttocks that cleared with antiviral therapy.¹⁰⁷ Perineal ulcers developed at 1 month of age in a patient who was biopsied after lack of response to numerous topical therapies. The biopsy demonstrated intranuclear inclusions and positive immunoperoxide staining for CMV.¹⁰⁶

Enteroviruses are well-recognized causes of vesicular exanthems and enanthems in infants and children. Enterovirus infections may occur congenitally or during neonatal life, particularly in the summer months. One infant with fatal neonatal echovirus 19 infection developed a hemorrhagic bulla associated with gangrene and necrosis of a portion of her hand and fingers.¹⁰⁸ After the newborn period, enteroviruses become a relatively frequent cause of vesicles and erosions. In typical hand, foot and mouth disease, the primary lesion is a small, oval, gray vesicle characteristically located on the hands, feet, mouth and diaper area. However, infants and children with atypical enteroviral exanthems, particularly those due to Coxsackie A6 infection have been reported with impressive, widespread vesicles and bullae (Fig. 10.9). These patients also develop erosions within skin affected by atopic dermatitis, a phenomenon referred to as ‘eczema coxsackium’.¹⁰⁹

Outbreaks of an acute, febrile *Aedes* mosquito-borne arboviral infection, Chikungunya, have been reported in India and Africa that can present with diffuse vesiculobullous exanthems in infants.^{110–112}

Cutaneous infestations

SCABIES

Scabies (see also Chapter 14) is a cutaneous infestation caused by the mite *Sarcoptes scabiei*. Clinically recognizable infection in infants less than 3–4 weeks old is rare, but becomes relatively common thereafter.¹¹³ An outbreak in a newborn nursery due to an affected healthcare worker has been reported.¹¹⁴ Vesicles and pustules are a more common presentation in infants than in older children or adults, and are often concentrated on the

medial feet, wrists, palms, and soles (Fig. 10.10). These areas may also demonstrate erythematous papules, nodules, and burrows. The eruption may also be concentrated in the axillae, periumbilical area and groin, but can also be very widespread (Fig. 10.11). Secondary bacterial infection can occur and should be suspected if bullae or significant honey-crusted areas are present. Young infants often lack significant pruritus, compared with older infants and children.

The diagnosis can be suspected on clinical morphology. In most cases, a history of itching or rash in other family members can be elicited. Whenever possible, the diagnosis should be confirmed with skin scrapings, which demonstrate a mite, eggs, or feces. The best lesions for scraping are burrows, intact vesicles, and pustules, but in young infants mites are also found in crusted areas. The diagnosis and management are discussed in Chapter 14.

INSECT BITE HYPERSENSITIVITY AND WELLS SYNDROME

Cutaneous hypersensitivity to insect bites (e.g. fleas, mosquitos) can result in vesicular, bullous or eroded pink papules in infants



Figure 10.10 Scabies infestation on the foot of a young infant, with vesicles, scale, and crusted areas.



Figure 10.11 Widespread scabies infestation in a 6-week-old infant. Multiple morphologies with crusts, wheals, nodules, and papules as well as small pustules are characteristically seen in severe cases. Axilla and nipple accentuation are common.



Figure 10.9 Enterovirus exanthem in a 2-year-old infant. More pronounced blistering – present on the arm – is a feature of Coxsackie CA6 infection, which was confirmed in this case.

and children. The lesions are usually grouped, discrete, urticarial, pink papules (often referred to as papular urticaria), but in some cases prominent vesicular or even bullous lesions may be present (Fig. 10.12). Itch is often very severe. Symptomatic relief with topical steroids and antipruritics can be helpful, but the ultimate solution is to find and eliminate the causative insect, which can be challenging.^{115,116}

Wells syndrome, or eosinophilic cellulitis, is an uncommon inflammatory skin disease that was reported in an infant who presented with bullae.¹¹⁷ Wells syndrome can be triggered by reaction to an insect bite in some cases, and has a good prognosis in children (see Chapter 11).

Transient skin lesions

ERYTHEMA TOXICUM NEONATORUM

Erythema toxicum neonatorum (toxic erythema of the newborn; see Chapter 7) is a benign and self-limited condition that primarily affects term infants and is rare in preterm infants or those weighing less than 2500 g.¹¹⁸ It is the most common cause of cutaneous pustules in term neonates.^{2,104,119,120} Most cases develop between 24 and 48 h of life, with 11% occurring before 24 h and 25% with onset after 48 h of life. Cases presenting at birth¹¹⁸ or as late as 10–14 days of life have been reported, but are unusual enough that clinicians should seriously consider other diagnoses.¹²¹

Four distinct skin lesions occur in varying combinations: erythematous macules, wheals (resembling flea bites), papules, and pustules (Fig. 10.13). Occasionally, lesions appear as small vesicles before becoming pustular. The trunk, buttocks, and proximal extremities are common sites of involvement.¹²⁰ The palms and soles are virtually never affected. Erythematous macules and wheals may vary in size from a few millimeters to several centimeters, with papules and pustules 1–2 mm in size superimposed on erythematous macules or wheals. The rash waxes and wanes, with previously involved skin returning to normal in a few hours to 1–2 days, with new lesions continuing to develop for several days. Mechanical irritation of the skin can precipitate the onset of new lesions. Spontaneous resolution of the eruption occurs without scarring.¹²⁰



Figure 10.13 Neonate with erythema toxicum. Note numerous erythematous wheals, papules and pustules scattered over the torso.

The diagnosis of erythema toxicum is usually made clinically but can be confirmed with Wright's stain of a pustule, demonstrating numerous eosinophils. Skin biopsy, while usually unnecessary, demonstrates eosinophilic infiltration of the outer root sheath of the hair follicle epithelium. In pustular lesions, eosinophils coalesce into an intraepidermal or subcorneal pustule, adjacent to a hair follicle. An upper dermal and perivascular eosinophilic infiltrate is also present.¹²²

The differential diagnosis of erythema toxicum includes neonatal pustular melanosis, congenital candidiasis, miliaria rubra, incontinentia pigmenti, and eosinophilic pustular folliculitis. The latter two conditions have eosinophilic inflammation, but can be differentiated by their distribution, their more chronic course, and with histopathology. The associated erythema and typical postnatal onset may help to distinguish erythema toxicum from pustular melanosis, but overlapping features and simultaneous occurrence have been reported.¹²³

Once the diagnosis has been established, no specific treatment is necessary. Parents can be reassured about the benign and noninfectious nature of the condition.

TRANSIENT NEONATAL PUSTULAR MELANOSIS

Transient neonatal pustular melanosis (TNPM; see also Chapter 7) is a relatively common condition of unknown etiology. Like erythema toxicum, it is more common in term infants and is unassociated with other abnormalities.¹²⁴ Unlike erythema toxicum, lesions are virtually always present at birth, though they are occasionally noted later. It is most common in black infants and uncommon-to-rare in other races.¹²⁵

Three types of lesions occur in TNPM: pustules with little or no underlying erythema; ruptured pustules manifesting as slightly hyperpigmented macules with a surrounding collarette of scale; and hyperpigmented macules without scale. Lesions vary in size from 1 to 10 mm, but are typically 2–3 mm. They may be solitary or grouped. Small satellite pustules may be present at the periphery of larger pustules (Figs 10.14, 10.15). More than one type of lesion may be present at the same time. The eruption may occur on virtually any part of the skin, but is most common on the forehead, behind the ears, under the



Figure 10.14 Transient neonatal pustular melanosis. Large pustules on the scrotum were present at birth. Note additional very small pustules on the thigh and at the base of the penis which are more typical findings. (Courtesy of David Lee, MD.)



Figure 10.12 Severe bullous reaction to insect bites mimicking bullous impetigo. More typical papules and clustering on the distal legs and ankles were clues to the diagnosis.



Figure 10.15 Transient neonatal pustular melanosis. Large pustule on the hand with tiny 'satellite' pustules may mimic infection. (From Frieden IJ. *Blisters and pustules in the newborn*. *Curr Probl Pediatr* 1989; 19:587.)

chin, on the neck and back, and on the hands and feet. The palms and soles may be affected.

The diagnosis of pustular melanosis is usually based on lesional morphology, time of onset, and the absence of other findings. Clues to clinical diagnosis are the extremely superficial nature of the pustules and the absence of underlying erythema.

Wright's stain often demonstrates polymorphonuclear neutrophils (PMN), with an occasional eosinophil, but in rare cases, eosinophils may predominate. Gram staining demonstrates PMNs but no bacteria. Skin biopsy, rarely necessary for diagnosis, demonstrates hyperkeratosis, acanthosis, and an intra-corneal or subepidermal pustule filled with PMNs, occasional eosinophils, and variable amounts of keratinous debris, serous fluid, and fragmented hair shafts.¹²⁴

The differential diagnosis of TNPM includes erythema toxicum, staphylococcal impetigo and other bacterial infections, congenital candidiasis, acropustulosis of infancy, and miliaria. These conditions can nearly always be differentiated by time of onset, lesional morphology, demonstration of PMNs on Wright's stain, and the absence of organisms on Gram stain and KOH preparations.

Once the diagnosis of TPNM has been established, no treatment is necessary. Pustules usually resolve over a few days, but hyperpigmented macules may last for several weeks to months before resolving.

STERILE TRANSIENT NEONATAL PUSTULOSIS

The term 'sterile transient neonatal pustulosis' was introduced by Ferrandiz and colleagues¹²³ to describe infants with clinical and histologic features of both erythema toxicum neonatorum and TNPM. They proposed that a clear-cut differentiation between these two conditions is not always possible. Although there may be overlap in some cases, most authors continue to use the diagnostic categories of erythema toxicum neonatorum and TNPM rather than combine the two together.

MILIARIA

Miliaria (prickly heat; see [Chapter 7](#)) is a relatively common finding in both newborns and older infants. In warm climates without air-conditioned nurseries, miliaria may be present in up to 15% of newborns,¹²⁶ but it is less common in temperate



Figure 10.16 Pustular miliaria rubra on the face of a 10-day-old infant. (Courtesy of Sarah Arron, MD PhD.)

climates. Two types of miliaria occur in the newborn period and both can also occur in older infants. *Miliaria crystallina* is due to blockage of the sweat duct at the level of the stratum corneum. Sweat accumulates beneath the stratum corneum, causing tiny flaccid vesicles that resemble dewdrops. *Miliaria rubra* is also due to blockage of the sweat duct in the stratum corneum, but the obstruction leads to focal leakage of sweat into the dermis, resulting in an inflammatory response, evident in the erythematous papules and pustules that are present clinically ([Fig. 10.16](#)).¹²⁷ Pustules may be more prominent in cases where there has been excessive warming in an incubator or occlusion of an area e.g., bandages, masks used in phototherapy, or occlusive garments or inappropriately heavy clothing ([Fig. 10.17](#)). Miliaria crystallina is occasionally present at the time of birth, whereas miliaria rubra is more common after the first week of life.^{127,128} In one study of Turkish neonates, miliaria crystallina was the most common form of miliaria, followed by rubra.¹²⁹

The most common locations for miliaria are the forehead and upper trunk. Lesions often become confluent and this, combined with location, time of onset, and a history of excessive warming, may help distinguish miliaria from other vesicular and pustular eruptions. Miliaria crystallina is also easily recognized because the dewdrop-like vesicles rupture easily with only slight pressure. Although the precise cause of miliaria is not known, an extracellular polysaccharide produced by some strains of *Staphylococcus epidermidis* may obstruct sweat delivery.¹³⁰

In cases where the diagnosis is uncertain, a skin biopsy can be performed. In miliaria crystallina, subcorneal vesicles are contiguous with underlying sweat ducts. In miliaria rubra, intraepidermal vesicles are due to epidermal edema. These vesicles, which are also in contiguity with a sweat duct, have an intravesicular and dermal chronic inflammatory infiltrate. No specific treatment is necessary for miliaria; the condition will disappear spontaneously if overheating is avoided.

Older infants and children can also develop miliaria particularly in warm climates.¹³¹



Figure 10.17 Miliaria rubra with prominent pustules. This morphology is more common if a dressing or clothing has previously occluded the affected area.

SUCKING BLISTERS

Sucking blisters result from vigorous sucking by the infant during fetal life. The lesions are always present at birth; they occur in approximately 1 in every 250 live births, and are not associated with other abnormalities.^{132–134} These bullae are usually flaccid, vary in size from 5 to 15 mm, and may evolve rapidly to become superficial linear or round erosions. Characteristic locations include the radial forearm, wrist, and hand, including the dorsal thumb and index fingers. The lesions may be unilateral or bilateral and symmetric.

The diagnosis can be suspected if typical skin changes are present at characteristic sites, without evidence of vesicles or bullae on other areas of the body. The infant usually confirms the diagnosis by demonstrating an insatiable appetite for the skin of their own forearms, wrists, and fingers. The lesions resolve without specific treatment within days to weeks.

NEONATAL CEPHALIC PUSTULOSIS (NEONATAL 'ACNE')

Although neonatal 'acne' has been considered common, the term 'neonatal cephalic pustulosis' has been proposed for this condition. This is at least in part to distinguish it from the infantile form of true acne vulgaris, characterized by variable mixtures of comedones, inflammatory papules and pustules, and nodules, which unlike neonatal acne usually presents after 1 month of age and can persist for months to years.¹³⁵ (See also Chapters 7 and 25.)

Cephalic pustulosis is characterized by a papulopustular facial eruption usually concentrated on the central and lateral cheeks, but the forehead, chin, eyelids, neck, upper chest, and scalp may also be affected (Fig. 10.18). The mean age of onset is 2–3 weeks, with some cases beginning as early as day 5 of life.¹³⁶ Cases can occasionally develop as late as 6–8 weeks of life, though arguably these have a tremendous amount of overlap with seborrheic dermatitis and miliaria rubra (Fig. 10.19). It is typically asymptomatic and unassociated with other medical conditions, but evolution to true infantile acne or seborrheic dermatitis has been described.¹³⁷ Several authors have proposed *Malassezia furfur* and *M. sympodialis* as causes of this condition; cultures of pustules have demonstrated both species, especially in severe cases.¹³⁶ However, these organisms are found on the skin under normal conditions and their role in causing this disease is still somewhat controversial. In another study, colonization of *M. furfur* did not correlate with development of neonatal cephalic pustulosis.¹³⁸

The diagnosis is usually made clinically, but Giemsa-stained smears can demonstrate fungal spores, as well as neutrophils and occasionally other inflammatory cells.¹³⁷ Special growth media are necessary to culture *Malassezia* species. Treatment with topical imidazole creams such as ketoconazole can result in resolution of the eruption, but the condition also frequently improves with low-potency topical corticosteroids such as hydrocortisone and also remits spontaneously after several weeks.

DIAPER EROSIONS

Transient, superficial erosions can occur in the diaper area (see also Chapter 17) between 1 and 14 days of life. These erosions are likely due to either perinatal trauma or the minor trauma

of normal diaper care, and their presence suggests that newborns – even if term – may have increased skin fragility compared with older infants.¹³⁹

In older infants, erosions or ulcerations may be seen due to severe irritant diaper dermatitis. A particularly dramatic presentation is that of large erosions caused by diarrhea from senna laxatives.^{140,141} Skin infections and infestations that cause pustules and vesicles in the diaper area in infants include scabies, *Staphylococcus*, *Streptococcus*, herpes simplex and *Candida*. Vesicular viral exanthems, such as hand, foot and mouth disease, often involve the diaper area. Less commonly, acrodermatitis enteropathica and Langerhans' cell histiocytosis can cause erosions in the groin in older infants. Lichen sclerosus in infants is rare, but can also manifest as hemorrhagic bullae or fissures in the genitalia.¹⁴⁰

IATROGENIC CAUSES OF EROSIONS AND ULCERATIONS

Many iatrogenic interventions can cause cutaneous erosions or, less commonly, ulcerations (see also Chapter 8).¹⁴² Scalp erosions can be due to intrauterine placement of fetal scalp electrodes for monitoring purposes. One prospective study of 535 monitored newborns found that 21% had very minor superficial lacerations that healed before discharge, and 18.7% had superficial lacerations still present at discharge. A rarer finding, scalp ulcerations, was present in 1.3% of cases.¹⁴³ These lesions are usually only a few millimeters in diameter, but occasionally measure up to 1–1.5 cm. They are sometimes confused with the lesions of aplasia cutis congenita. A pustular eruption has also been reported as a sequela of vacuum-assisted delivery. Unusual scalp changes (e.g., pustules, erosions, ulcerations) in the neonatal period should always lead to consideration of possible neonatal herpes infection.⁸⁹

Transcutaneous pulse oximetry may rarely lead to blistering or erosions, particularly if a defective device results in overheating of the skin leading to a thermal burn, or from sustained pressure from a probe left in one location for over 24 h.¹⁴⁴ Erosions or crusted areas may also occur on the heel, following multiple heel punctures to draw blood.

Scald burns represent a relatively common form of childhood injury, but are rare in the neonatal period and in this age group, may have occurred accidentally in medical settings.¹⁴⁵ In patients outside of the newborn period but younger than 2 years of age, burns are more likely to be intentional than accidental, so one should always carefully investigate for potential child abuse or neglect.^{146,147}

Uncommon and rare causes of vesicles and pustules

INFANTILE ACROPUSTULOSIS

Infantile acropustulosis (IA) is characterized by the development of extremely pruritic vesicles and pustules concentrated on the hands and feet. Lesions may be present at birth, but more often develop in the first weeks or months of life.^{148,149} Two distinct variants of IA have been identified. The less common variant is that which arises spontaneously, usually with onset early in infancy. This form typically develops at a few weeks to months of age, and is more common in infants of African descent, though it can occur in all races (Fig. 10.20).¹⁵⁰ Boys are



Figure 10.18 Cephalic pustulosis. Profuse cases like this one can sometimes be confused with other causes of vesicles and pustules. (Courtesy of Antonio Torrelo, MD.)



Figure 10.19 Cephalic pustulosis on the cheeks and chin of a 3-week-old infant.



Figure 10.20 Acropustulosis of infancy. (From Frieden IJ. Blisters and pustules in the newborn. *Curr Probl Pediatr* 1989; 19:591.)



Figure 10.21 Infantile acropustulosis following severe scabies infestation. Differentiation from recurrent or persistent scabies can be challenging, but over time the diagnosis becomes more obvious.

more commonly affected. An association with atopy has been reported in some patients and families. The other, more common form of AI is that which occurs after scabies infestation, also known as ‘post-scabetic acropustulosis.’ It has similar clinical features to spontaneously-arising AI but has also been reported in older children. Post-scabetic acropustulosis usually follows scabies infestation that has been either severe in degree or present for a prolonged period (Fig. 10.21). Cases are particularly common in international adoptees.¹⁵¹

In both forms of AI, the eruption waxes and wanes, with skin lesions appearing in crops every few days to weeks, lasting for 5–10 days. The eruption is intensely pruritic and infants too young to scratch may instead seem irritable and rub their feet vigorously against bedding. Lesions are initially tense, and then flatten, developing scale and postinflammatory hyperpigmentation. They are located on the palms and soles, dorsal hands and feet, as well as the sides of the fingers and toes. Scattered lesions may also be located on the ankles and wrists, and occasionally papules occur at more distant sites, such as the chest, back, and abdomen. Rare cases of IA in association with eosinophilic pustular folliculitis have also been reported.¹⁵²

The diagnosis can often be made clinically, or may be confirmed with either direct smears from vesiculopustular lesions or via skin biopsy. Scrapings of lesions show numerous PMNs and occasional eosinophils. Skin biopsy demonstrates an intraepidermal or subcorneal pustule filled with neutrophils, eosinophils, or both. The earliest histopathologic changes are focal vesiculation and degeneration of keratinocytes with cell necrosis.¹⁵³ Peripheral eosinophilia is occasionally present.¹⁵⁴

The major differential diagnosis of infantile acropustulosis is actual scabies infestation. Careful physical examination, family history, and multiple skin scrapings may be necessary to differentiate the two. As mentioned, the condition may actually be a sequela of scabies infestation, even after adequate anti-scabetic treatment, adding further diagnostic confusion.^{151,155} Other conditions in the differential diagnosis include dyshidrotic eczema, pustulosis palmaris et plantaris, congenital candidiasis, which is only present within the first days of life and typically more widespread, and neonatal pustular melanosis,



Figure 10.22 (A) Eosinophilic pustular folliculitis on the scalp. (Courtesy of Angela Hernandez-Martin, MD.)

which is not pruritic and does not occur beyond the immediate newborn period.

Acropustulosis of infancy spontaneously remits over time with episodes gradually diminishing in intensity. Very potent topical corticosteroids (class I or II) are the initial treatment of choice and should be used as soon as an incipient flare is noted. Because high-potency topicals are needed, they should be used intermittently, not continuously, to avoid localized atrophy or systemic absorption.¹⁵⁵ If symptoms are severe, oral antihistamines at maximum doses for weight can be used to control pruritus. Dapsone 1–2 mg/kg per day has been used for severe cases, but is generally not necessary, and should be used with caution because of the risk of methemoglobinemia and other adverse effects.¹⁴⁹

EOSINOPHILIC PUSTULAR FOLLICULITIS

Eosinophilic pustular folliculitis (EPF) is a rare disorder, however a case series of 15 infants and review of 61 reported cases published in 2012 provided important information regarding the clinical features, prognosis and recommendations for treatment.¹⁵⁶ EPF is more common in males than females (ratio 4:1). Onset in infancy occurs before age 14 months in 95% of patients with a mean age of onset of 6 months. The scalp is the principal site of involvement; however, the majority (65%) of patients also have other areas of skin involvement.¹⁵⁶ Several cases have been reported in young infants, including a few cases with onset at birth or in the first few days of life (Figs 10.22A,B, 10.23).^{157–160}

Lesions of EPF consist of itchy, isolated or clustered papules, papulo-pustules and vesicles on an erythematous base. They may evolve with crusting and heal with scarring. Pruritus is present in more than three-quarters of patients but not in all cases. Facial edema is a rare finding. Recurrent crops are typical with a waxing and waning course that lasts from a few months up to several years. However, most cases resolve by 3 years of age (mean 25.3 months; median 18 months).^{156,160} While most infants with EPF do not have an immunodeficiency, similar and overlapping findings can be seen in hyper-IgE syndrome and other conditions with immune dysregulation. Blood eosinophilia is present in approximately 80% of cases. IgE levels may occasionally be elevated as well.



Figure 10.22 (B) Eosinophilic pustular folliculitis in this patient also demonstrates many scattered papules in areas other than the scalp.



Figure 10.23 (A) Eosinophilic pustular folliculitis on the scalp of an 11 month-old infant. Lesions also occurred intermittently on the extremities. (B) Eosinophilic pustular folliculitis on the scalp.

When biopsies or smears are performed, tissue eosinophilia is virtually always present. Typically, there is a dense diffuse periadnexal and perifollicular eosinophilic dermal infiltrate, however not all cases have proven follicular involvement.¹⁵⁶ Flame figures are occasionally present. While the histopathologic findings are not entirely specific, taken together with clinical context, they can lead to a specific diagnosis. The differential diagnosis in neonates includes hyper-IgE syndrome, transient neonatal pustular melanosis, erythema toxicum neonatorum, Langerhans' cell histiocytosis, and acropustulosis of infancy. Mid-potency topical corticosteroids can be very effective in controlling symptoms.¹⁵⁶ Topical tacrolimus has also reportedly been effective.¹⁶¹ Oral antibiotics are often used because of confusion with bacterial infection, and may be effective in some cases, possibly due to their anti-inflammatory effects. Oral cetrizine has also reportedly been helpful in some cases.¹⁵⁶

EROSIVE PUSTULAR DERMATOSIS OF THE SCALP

Erosive pustular dermatosis of the scalp is rare in neonates and infants.¹⁶² It is most often reported in adults with either severe scalp injuries or severe chronic sun damage. However, neonates can develop this condition after severe caput succedaneum or halo-ring scalp injury, presumably due to damage to the scalp and hair follicles during a difficult delivery (see also [Chapter 8](#)). Over the ensuing several days to weeks, the inflammation evolves with pustules, scaling, and crusting developing in injured and scarred areas of the scalp. The clinical features of erosive pustular dermatosis of the scalp have also been described in an infant with Klippel–Feil anomaly.¹⁶³ This condition is remarkably similar to the severe scalp erosions and pustules seen in infants with Hay–Wells and Rapp–Hodgkin ectodermal dysplasias (see below). Infants with erosive pustular dermatosis improve with application of potent topical steroids but not usually with oral or topical antibiotics, unless secondary bacterial infection is present. Scarring alopecia is a sequela in all affected infants.¹⁶²

LANGERHANS' CELL HISTIOCYTOSIS

Langerhans' cell histiocytosis (LCH; see also [Chapter 28](#)) presents either as a generalized eruption or as solitary or multiple nodules. At birth or in the early neonatal period, LCH presents with crusting, pustules, erosions, or ulcerations. Later in infancy, LCH more often presents with hemorrhagic papules or nodules, but ulcerations or erosions are not rare ([Fig. 10.24](#)). The most dramatic form of presentation in the neonatal period has been called 'congenital self-healing reticulohistiocytosis' or Hashimoto–Pritzker disease.^{164–167} In this form, skin lesions are virtually always present at birth, however new lesions may continue to erupt over the first several weeks. The eruption may affect any area of the body, including the palms and soles. Numerous morphologic characteristics have been reported, including erythematous papules, hemangioma-like papules, nodules, pustules, vesicles, bullae, necrotic and hemorrhagic bullae, discrete erosions, widespread eroded patches, and ulcerations.^{168–172} Lesions vary in size from a few millimeters to several centimeters, but in most cases with vesicles or pustules, smaller cutaneous lesions predominate. Petechiae, atrophy, and milia may occasionally be present, and anetoderma-like scarring has been reported.¹⁷³ Occasionally, lesions disappear so

quickly that none are present at time of dermatology evaluation. If clinically typical for 'self-healing' LCH, serial follow-up to monitor for recurrence and extracutaneous disease is recommended.¹⁷⁴ The clinical presentations in older infants and children differ somewhat from those of neonates in that rapidly self-resolving and solitary ulcerated nodules are less common (see [Chapter 28](#)).

If LCH is suspected in a neonate with a vesiculopustular eruption, a preliminary diagnosis can be made via Tzanck preparation, which demonstrates histiocytes with reniform nuclei and abundant cytoplasm.¹⁷⁵ Confirmatory skin biopsy reveals an infiltrate of histiocytes, with large cells and irregularly shaped vesicular nuclei and eosinophilic cytoplasm in the upper dermis. The histiocytes may also invade the epidermis focally. Occasional lymphocytes and eosinophils may be present. The diagnosis should be further confirmed with an S-100 stain, immunohistochemical markers, and/or electron microscopy, to evaluate for the presence of Langerhans' cells.¹⁷⁶ The Histiocyte Society has established guidelines to assist in the diagnosis and evaluation of LCH.¹⁷⁷ All patients with suspected LCH must undergo a thorough physical examination and laboratory evaluation, including CBC, liver function tests, urine osmolality, skeletal survey, and chest X-ray. Referral to oncology for consideration of ancillary studies such as bone-marrow aspiration or biopsy is recommended.

The differential diagnosis of congenital self-healing histiocytosis includes intrauterine herpes simplex infection, congenital candidiasis, neonatal varicella, and intrauterine graft-versus-host disease.

As noted, neonatal cases are often self-resolving but numerous cases with relapse or progression have been reported.^{178,179} Because cutaneous or even systemic relapse may occur months to years later, long-term follow-up and monitoring is required.^{159,180}

Cases with onset *after* the newborn period have a high risk of associated extracutaneous disease, estimated to be present in the majority of cases of LCH in children under 4 years of age. Risk stratification is based on whether single or multiorgan involvement is present; if multiorgan disease is present, further stratification is based on whether organ dysfunction is present.¹⁷⁷

INCONTINENTIA PIGMENTI

Incontinentia pigmenti (IP; see [Chapter 29](#)) is a multisystem disease, with X-linked dominant inheritance. The mutation for IP is located at Xq28, affecting the NFκB essential modulator (NEMO) gene.^{181,182} Skin lesions are present at birth in 50% of cases and occur within 2 weeks in 90%, usually beginning as a vesicular eruption that evolves into linear streaks of clear or yellow confluent vesicles, following the lines of Blaschko ([Figs 10.25, 10.26, 10.27](#)).¹⁸³ The eruption is most common on the trunk, extremities, and scalp, often sparing the face. The vesicular phase may wax and wane for up to a year and occasionally recur, but individual lesions usually resolve within 1–2 weeks. As the initial vesicular phase subsides, a verrucous stage consisting of hyperkeratotic streaks usually occurs, followed by a pigmented stage with streaky, reticulated pigment forming a 'marble-cake pattern' that fades over many years. The final stage is that of hypopigmented, atrophic patches, usually on the extremities, which may be subtle and unappreciated. Because these stages may overlap in time, as well as occurring in utero, vesicular lesions may be seen in conjunction with verrucous or



Figure 10.24 Congenital Langerhans' cell histiocytosis presenting as small crusted erosions. (Courtesy of Linda Beets-Shay, MD.)



Figure 10.26 Incontinentia pigmenti. The extensive linear blistering in this case, which is more pronounced than is usually seen, can resemble other causes of neonatal vesicles and bullae.



Figure 10.27 Incontinentia pigmenti. Two different infants with linear crusting and erosions due to incontinentia pigmenti.



Figure 10.25 Incontinentia pigmenti with pustules and crusting on the arm and leg of 2-week-old infant. Note the linearity of the lesions.

hyperpigmented lesions. Additional cutaneous changes include patchy, scarring alopecia, nail dystrophy and abnormalities in sweating.

Diagnosis is made by skin biopsy, which demonstrates an edematous (spongiotic) epidermis with eosinophilic infiltration, dyskeratosis, and eosinophilic microabscesses. The linear patterning of IP may not be as striking early in the course of disease, becoming more obvious over time.¹⁸⁴ Atypical presentations as well as lack of familiarity with the broad differential diagnosis of vesiculopustular diseases in neonates often leads to initial misdiagnosis, particularly as neonatal HSV infection or other conditions such as erythema toxicum, varicella, bullous impetigo, and diffuse cutaneous mastocytosis.¹⁸⁵ Rare cases of coexistent neonatal HSV infection and IP have been reported.^{186,187}

HYPERIMMUNOGLOBULIN E SYNDROME AND DOCK8 DEFICIENCY

Hyperimmunoglobulin E syndrome (HIES) – also known as Job syndrome – and DOCK8 deficiency are primary immunodeficiencies, which are both characterized by eczematous rash, cutaneous staphylococcal abscesses, elevated IgE levels and eosinophilia. HIES is usually sporadic or autosomal dominant with gene mutations identified in the STAT3 gene, whereas DOCK8 deficiency is an autosomal recessive disorder. While both can have onset of skin manifestations in early infancy, 80% of cases of HIES have a neonatal onset with a mean age of onset of 7 days. Only a minority of DOCK8 cases present neonatally.¹⁸⁸

The eruption of HIES begins as pink papules, many of which very quickly begin to ooze or become pustular. In the vast majority of cases, the face and scalp are the initial sites of involvement but over time, it can spread to other sites (Fig. 10.28).^{189,190} The cutaneous eruption is not entirely specific, however, and the differential diagnosis at this age includes several other conditions, including neonatal cephalic pustulosis, erythema toxicum neonatorum, eosinophilic pustular folliculitis, and atopic dermatitis. Clues to diagnosis include: the persistent – albeit fluctuating – nature of the rash, the propensity for recurrent *Staphylococcus aureus* infection, pruritus,



Figure 10.28 Hyper-IgE syndrome. Numerous papules and crusted areas are evident on the forehead of this young infant. (Courtesy of Dr Sarah Chamlin.)

extension to other body sites and poorer than expected response to topical therapies for atopic dermatitis.

During infancy, both HIES and DOCK8 deficiency usually have a pruritic dermatitis, which can be indistinguishable from chronic atopic dermatitis in appearance. However, the severity and associated features such as peripheral eosinophilia and the development of recurrent staphylococcal furuncles and abscesses may help point to one of these immunodeficiencies.¹⁹⁰ IgE levels may not be helpful – levels during infancy, although higher than in normal age-matched controls, are often <2000 IU/mL and may not rise until after 1 year of age. Despite the name ‘hyper-IgE syndrome’ levels may actually be lower than in cases of severe atopic dermatitis.^{190,191} Skin biopsy in HIES can demonstrate eosinophilic folliculitis. In both HIES and DOCK8 deficiency, other problems can develop over time: mucocutaneous candidiasis, sinopulmonary infections, severe food allergies, and asthma. Features of HIES not typically seen in DOCK8 deficiency include coarse facies, osteopenia, increased fractures, joint hyperextensibility, and retention of deciduous teeth.¹⁸⁸ See Chapter 15 for further discussion of these conditions.

PUSTULAR ERUPTION IN MYELOPROLIFERATIVE DISORDER OF DOWN SYNDROME

A pustular eruption – particularly located on the face and in areas of skin injury – has been reported in several infants with trisomy 21 (Down syndrome), in association with a myeloproliferative disorder. Typically, the eruption begins in the first few days to weeks of life. It most often involves the face, but can spread to the body and become fairly extensive.^{192,193} It resolves spontaneously over days to weeks. Pathergy – the tendency to aggregate at areas of skin injury – has been reported in several cases (Fig. 10.29).^{192,194} Tzanck preparation stain may be helpful in diagnosis, demonstrating immature myelocytes and promyelocytes.¹⁹³ Skin biopsies usually demonstrate intraepidermal spongiosis and inflammation with a perivascular infiltrate of immature myeloid cells, reminiscent of leukemia cutis. The myeloproliferative disorder of Down syndrome can evolve to myeloid leukemia. It can also resolve spontaneously, but affected infants have an increased risk of subsequent development of



Figure 10.29 Extensive vesiculopustular eruption in the setting of leukemoid reaction associated with Down syndrome. (Courtesy of Drs Alanna Bree and Elaine Siegfried.)

myeloid leukemia.¹⁹⁴ This eruption has also been reported in infants with high peripheral white blood count without obvious Down syndrome who are subsequently shown to have mosaic forms of Down syndrome affecting the bone marrow.^{192,195}

NEONATAL EOSINOPHILIC PUSTULOSIS

A similar pustular eruption to that described with Down syndrome and myeloproliferative disorder has been described in at least two other children with marked peripheral eosinophilia. Both were monozygotic twins and one was documented to have received numerous transfusions and GCSF for severe anemia from twin-to-twin transfusions. In these cases, the pustules' onset was during the newborn period but the infants had continued skin lesions until several months of life with resolution as the eosinophil count normalized.^{196,197}

PUSTULAR PSORIASIS AND DEFICIENCY OF INTERLEUKIN 1 RECEPTOR ANTAGONIST

Pustular psoriasis is very rare in the newborn period and infancy but has been reported with onset as early as 20 days of life. Skin biopsies and follow-up are necessary to help confirm the diagnosis.¹⁹⁸ Pustules are superimposed on erythematous skin often with associated scaling. Annular pustular psoriasis is a well-reported albeit uncommon presentation of psoriasis in infants and young children. It can mimic tinea corporis and other annular eruptions and over time can develop into more generalized pustular psoriasis.¹⁹⁹

A rare condition known as 'deficiency of interleukin 1 receptor antagonist' (DIRA) can also present as early onset of a pustular eruption either in the newborn period or first few months of life. Other findings include failure to thrive, joint swelling, osteolytic bone lesions and fever.²⁰⁰ Both conditions are discussed in more detail in [Chapter 16](#).

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis (AGEP) is characterized by the sudden onset of fever, widespread erythroderma

with minute (1–2 mm) pustules. The pustules are sterile and are not accentuated in hair follicles. To our knowledge, this condition has not been reported in neonates, but several cases have been reported in young infants.^{201,202} In older children and adults, the usual cause is a medication, particularly beta-lactam antibiotics; however, other medications or triggers like vaccinations, viral illnesses, and spider bites may be causative. Medications may be less frequent as triggers in young infants. The differential diagnosis of AGEP includes toxin-mediated erythema (e.g., Kawasaki or toxic shock syndrome), pustular psoriasis, miliaria pustulosa, and allergic contact dermatitis, or miliaria. Treatment includes supportive care and stopping any medications which could be causative. AGEP usually resolves spontaneously within a few days to 2 weeks after removal of the drug. Supportive treatment is recommended, including antihistamines and bland emollients.

NEONATAL BEHÇET DISEASE

Behçet disease rarely presents in the neonatal period: in one French study, four out of 55 pediatric cases had onset of symptoms before the age of 1 year.²⁰³ A few cases of neonatal Behçet disease acquired transplacentally from affected mothers have been described. Skin manifestations develop within 1 week of life and generally resolve by 2–3 months of age. These infants present with oral and/or genital ulcerations, and may develop pustular or necrotic skin lesions, primarily on the hands and feet and at sites of trauma.²⁰⁴ Although most infants have no systemic symptoms, two cases with severe systemic manifestations have been described.^{205,206} One child of a mother with known Behçet disease died of neurological complications at 9 days of age. Another infant had bloody diarrhea and vasculitis, which responded to systemic corticosteroids. Of note, the mother of this infant had not been diagnosed with Behçet disease prior to her delivery. She had developed oral and genital ulcerations during pregnancy that resolved and then recurred when the infant was 24 days old.²⁰⁵ With this exception, infants with neonatal-onset Behçet disease were diagnosed because of a known diagnosis in the mother. A primary consideration in the differential diagnosis of neonatal Behçet disease is HSV infection; viral cultures and maternal history of Behçet's can help distinguish these entities.

MASTOCYTOSIS

Mast cell disease (see also [Chapter 28](#)) causing blisters of the skin in infants occurs in three forms: (1) discrete nodules, known as solitary mastocytomas; (2) multiple papules and plaques (maculopapular cutaneous mastocytosis, or urticaria pigmentosa); and (3) widespread infiltration of the skin (diffuse cutaneous mastocytosis). Solitary mastocytomas typically present as slightly infiltrated plaques or nodules – often yellow-orange-brown in color. They may develop erythema and wheals especially with friction. Edema, blistering or crusting can ensue, most typically in the center of the lesion ([Fig. 10.30](#)). Diffuse cutaneous mastocytosis (DCM) is a much rarer condition. Evidence of disease can be present at birth or develop in the first weeks to months of life. In DCM, blisters can develop initially on normal-appearing skin, making the clinical diagnosis difficult until thickened, leathery skin becomes evident ([Figs 10.31, 10.32](#)). DCM has a worse prognosis for chronic course and risk of systemic involvement than other forms of mastocytosis.²⁰⁷ In



Figure 10.32 Diffuse cutaneous mastocytosis presenting with widespread blistering. (Courtesy of Dr Sarah Chamlin.)

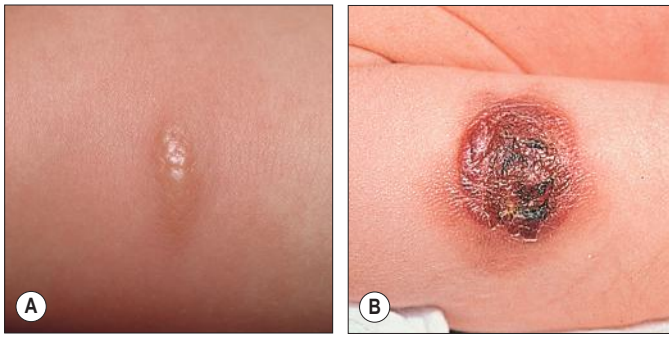


Figure 10.30 Mastocytomas. (A) Edema and vesiculation overlying a solitary mastocytoma in an 8-month-old infant. (B) Blistering and crusting in a mastocytoma on the arm. (Courtesy of Neil Prose, MD.)



Figure 10.31 Diffuse cutaneous mastocytosis. Tense blisters, areas of skin thickening, and hypopigmentation on the anterior torso of this young infant.

all three clinical forms, blistering is at the level of the lamina lucida.²⁰⁸ Serum tryptase can correlate with extent of cutaneous involvement and be a surrogate marker for disease severity.²⁰⁹ Familial cases with apparent autosomal dominant inheritance have been reported in both urticaria pigmentosa and DCM.²¹⁰ The differential diagnosis of bullous mastocytosis includes staphylococcal scalded skin syndrome, toxic epidermal necrolysis, epidermolysis bullosa, bullous congenital ichthyosiform erythroderma, and erythema multiforme.^{207,208,211}

BLISTERING CAUSED BY MATERNAL BULLOUS DISEASE

Blistering can occur in neonates born to mothers with autoimmune blistering disease mediated by IgG. This finding has been reported in several IgG-mediated diseases: pemphigoid gestationis (formerly called herpes gestationis), pemphigus vulgaris,



Figure 10.33 (A,B) Neonatal pemphigus vulgaris. Erosions and crusting are due to transplacental maternal autoantibodies. (Courtesy of Lee Nesbitt.)

pemphigus foliaceus,^{212–221} and epidermolysis bullosa acquisita.²²² IgG crosses the placenta, leading to fetal/neonatal involvement. Blistering is virtually always present at birth. Lesional morphology depends on the nature of maternal disease, causing a similar disease in the fetus, ranging from tense blisters to flaccid bullae or widespread areas of erosion (Fig. 10.33). The severity of neonatal skin disease varies from only a few lesions to widespread disease. Infants may be born prematurely. The diagnosis is usually obvious because of a maternal history of an autoimmune blistering disease. Most mothers have active disease during their pregnancy, but there have been rare reports of affected infants born to women with inactive disease.²²³

Diagnosis can be confirmed with skin biopsy and direct immunofluorescence on the infant's skin. A major differential diagnosis is epidermolysis bullosa, but a maternal history of an immunobullous skin helps in diagnosis. Once the diagnosis is made no specific therapy is needed, but topical petrolatum and/or antibiotics may help avoid secondary infection.²¹⁵ New blisters do not usually occur after the newborn period. If blistering is extensive, the infant should be watched closely for signs of cutaneous or systemic infection. Systemic corticosteroids should be considered only in extremely severe cases.

In rare cases, newborns can develop *de novo* autoimmune blistering diseases, such as bullous pemphigoid and chronic bullous disease of childhood but onset of these diseases is typically during infancy. These conditions are discussed in [Chapter 11](#).

NEONATAL LUPUS ERYTHEMATOSUS

Neonatal lupus erythematosus (NLE; see also [Chapter 20](#)), caused by the fetal and neonatal effects of transplacental maternal autoantibodies, including SS-A, SS-B, and U1-RNP can – in rare cases – present with widespread erosions or crusting.^{224,225} Most of these cases present at birth as a form of ‘congenital LE.’ Erosions may result from the shearing of atrophic epidermis from the underlying dermis during the birth process. Ulceration of the leg at birth with a background of livido reticularis, followed by transient bullae developing in the first days of life has been reported,²²⁶ as has NLE with vesicles and bullae with infiltrative plaques and central vesicles.²²⁷

The diagnosis can be suspected particularly if additional areas of atrophic or discoid skin lesions are present. Facial skin is often affected. Skin biopsy shows epidermal atrophy and a vacuolar interface dermatitis, which may have associated increased dermal mucin. The mothers of affected infants are usually asymptomatic. Serology tests of both mother and infant should be obtained, looking specifically for serologic markers of NLE. If NLE is suspected, infants should be carefully examined and an ECG, CBC, platelet count, and liver function tests should be obtained.

TOXIC EPIDERMAL NECROLYSIS AND BULLOUS ERYTHEMA MULTIFORME

Toxic epidermal necrolysis (TEN) and erythema multiforme (EM) (see [Chapter 20](#)) are extremely rare in the newborn period. Scattered cases of EM have been described, but most have no associated blistering. A 25-day-old neonate was reported with biopsy-proven erythema multiforme preceded by upper respiratory infection. Clinical features included bullae on the face and erosions on the palate, but without a generalized, confluent eruption.²²⁸

The few cases of TEN reported in early infancy have been in premature infants and caused by Gram-negative infections.²²⁹ Graft-versus-host disease can also cause TEN and may occur at birth because of intrauterine passage of maternal cells to an immunodeficient fetus.^{230,231} Infants with TEN may present with irritability, temperature instability, and diffuse cutaneous erythema, followed by flaccid blisters and erosions ([Fig. 10.34](#)). The diagnosis can be confirmed by skin biopsy, which demonstrates extensive, full-thickness epidermal necrosis and minimal to absent dermal inflammation. The epidermal cleavage is located at the dermoepidermal junction or in the mid to lower epidermis. A frozen section can be performed for rapid diagnosis.²³²

The differential diagnosis includes staphylococcal scalded skin syndrome and intrauterine epidermal necrosis.²³³ Management of TEN at any age is difficult, and the mortality rate is high, especially in young infants. The cause of the eruption should be identified and, in the case of graft-versus-host disease or sepsis, treated appropriately. Treatment of the skin parallels that of patients with widespread epidermolysis bullosa (see [Chapter 11](#)). TEN is a potentially life-threatening condition at

any age, because the skin necrosis causes the functional equivalent of severe first- and second-degree burns. The situation is even worse in the newborn period because of decreased immune defenses and a more tenuous balance of fluids and electrolytes. The prognosis is poor in the neonatal period: most affected neonates have died either from TEN or other causes.²²⁹

Although very uncommon, older infants can develop TEN or other widespread blistering hypersensitivity reactions such as Stevens–Johnson syndrome due to drugs (antiepileptic, antibiotic) or infections acquired in the community or at home such as HSV.^{234,235}

INTRAUTERINE EPIDERMAL NECROSIS

This rare condition is characterized by widespread epidermal necrosis. It has been described in a few premature infants. Skin changes were present at the time of delivery, and all affected infants have died shortly after birth.²³³ Widespread areas of erosion and ulceration were noted, without vesicles or pustules, and mucous membranes were spared. Histopathology of the skin demonstrated extensive epidermal necrosis and pilosebaceous follicular calcification. Autopsy study demonstrated brain infarcts and leukomalacia, as well as cardiomegaly and renal tubular necrosis. The etiology of this condition in these cases is unknown. A fourth case with similar clinical and histopathologic findings was associated with congenital herpes simplex infection.²³⁶ The differential diagnosis includes intrauterine infection, epidermolysis bullosa, acute graft-versus-host disease with TEN, and congenital erosive and vesicular dermatosis.

CONGENITAL EROSION AND VESICULAR DERMATOSIS

More than a dozen cases of this condition have been reported.^{237–242} Nearly all of the infants were premature. Reports from the neonatal period describe erosions and vesicles at birth, as well as crusting, generalized ‘scalded skin-like,’ and erythematous areas, which eventually healed with reticulate and supple scarring. Additional variably reported features include collodion membrane, transparent areas of skin, and a reticulated vascular pattern with subsequent ulcerations. In some cases, the face, palms, and soles are spared. Erosions and ulcerations heal with scarring, usually by 1–2 months of age. The resulting scarring is reticulated and often covers the majority of the skin surface. Ongoing but milder, nonscarring blistering can continue for years.^{239,243} Other more variable mucocutaneous findings include scarring alopecia of the scalp and eyelashes, scarring of the tongue, absent or hypoplastic nails, and heat intolerance. Mental retardation, cerebral atrophy, hemiparesis, and retinal scars have also been described.

The cause of the condition is unknown, although some have speculated that an intrauterine infection, as yet unidentified, might result in these findings. The diagnosis has usually been made in retrospect, with biopsy specimens demonstrating scar formation and loss of eccrine structures. There are few cases with histology during the neonatal period. Those reports have demonstrated an eroded epidermis with a dense neutrophilic infiltrate²⁴⁴ or discrete vesicles in the superficial papillary dermis with mildly increased dermal collagen.²³⁹ The differential diagnosis includes the erosive form of neonatal lupus, acute intrauterine graft-versus-host disease, bullous ichthyosis, intrauterine epidermal necrosis, and a variety of intrauterine infections,



Figure 10.34 Toxic epidermal necrolysis. Most documented cases in very young infants are due to Gram-negative infections, but this case was as a result of intrauterine graft-versus-host disease. In older infants, drugs are the most common cause. (Courtesy of Mary L. Williams, MD.)

especially HSV and varicella. All neonates with the clinical findings of vesicles and atrophy in the newborn period should have thorough investigations, including cultures, biopsies, and serologic evaluations for infection, and should be followed closely, especially for neurologic deficits. There is no specific treatment, although careful wound care is essential. One study found silicone dressings helpful.²⁴²

LIPOID PROTEINOSIS

Lipoid proteinosis is a rare disorder caused by homozygous or compound heterozygous mutation in the ECM1 gene. Classic features include beaded eyelid papules and laryngeal infiltration with hoarseness. Several cases with papulovesicles or erosion, particularly on the face, with onset in early infancy have been reported. These often result in depressed acneiform scars. The diagnosis can be confirmed both with characteristic histology, demonstrating a widespread deposition of hyaline material and disruption/reduplication of basement membrane, or with specific genetic testing.²⁴⁵

PYODERMA GANGRENOSUM

Pyoderma gangrenosum (PG), a disorder characterized by the spontaneous onset of skin ulcerations, has rarely been reported in infants less than 2 years of age. To date, only one case with neonatal onset has been reported. In this infant, the ulcers began to develop at 2 days of age. Lesions were most prominent in the groin and buttocks, as has been the case in most other infants (Fig. 10.35).²⁴⁶ The lesions are sharply demarcated ulcerations, which usually arise without prior vesiculation or pustules, and have characteristically undermined borders. Ulcers can appear at sites of trauma and extend with further injury to the skin, a phenomenon known as pathergy.^{247,248} A 1-year-old infant presenting with PG in the diaper area ultimately diagnosed with Crohn disease was described.²⁴⁷ The disease can recur. In older infants and children, PG has been associated with underlying infection, inflammatory bowel disease, leukemia, myelodysplastic syndrome, autoimmune neutropenia, arthritis, and less commonly immunodeficiency.^{249–251} The diagnosis, which is one of exclusion, is made by correlating typical clinical



Figure 10.35 Pyoderma gangrenosum. Multiple ulcerations in the perineum are evident.

features with histopathology demonstrating a neutrophilic infiltrate without evidence of infection, vasculitis, or other causes of ulceration. The differential diagnosis includes ecthyma gangrenosum, noma neonatorum, HSV infection, and ulcerations arising in hemangioma precursors or in lesions of incontinentia pigmenti.²⁵²

The initial treatment of choice is intralesional or systemic corticosteroids, but biological and cytotoxic agents, cyclosporine and sulfones have been used to control disease.²⁵³

NOMA NEONATORUM

Noma neonatorum is a gangrenous disease that has been described mainly in developing countries, with *Pseudomonas aeruginosa* septicemia implicated as a causative agent in the majority of cases.^{49,254,255} The clinical features in these cases include the abrupt onset of gangrenous, ulcerative skin lesions affecting the nose, lips, mouth, anus, scrotum, and eyelids. In severe cases, the ulcerations can be mutilating, resulting in bone loss and extensive deformity. Predisposing factors include prematurity, low birthweight, malnutrition, and previous illness, although previously well, term infants have been reported.^{255,256} There is some controversy about whether this is an entity distinct from neonatal ecthyma gangrenosum.⁴⁹ Although many neonatal cases undoubtedly represent primary *Pseudomonas* infection of the skin, other etiologies may be responsible in some cases, as in one preterm infant with fatal *E. coli* sepsis.²⁵⁷ Similar ulcerations have been described in several Native American children with severe combined immunodeficiency.²⁵⁸ The presence of oral and perineal ulcerations in newborns and young infants should prompt a thorough search for infectious and immunologic causes as possible etiologies.

PHYTOPHOTODERMATITIS

Phototoxic reactions to furocoumarins from plant exposure can present in infants and toddlers as vesicles, bullae, and erosions, often accompanied by streaky erythema or bizarrely shaped hyperpigmentation.²⁵⁹ Hand-print patterns from parents touching their children with the substance on their hands can result in confusion with bruising, and concern for child abuse. Phytophotodermatitis in children has been reported as a result of contact with lemons and limes, cow parsnip, and hogweed.^{259–261}

ACRODERMATITIS ENTEROPATHICA AND ACRODERMATITIS 'DYSMETABOLICA'

Acrodermatitis enteropathica (AE; see Chapter 17) is caused by zinc deficiency and can present in the first few weeks to months of life, though usually not before 4 weeks of age. It can result either from inadequate zinc intake or as an autosomal recessively inherited defect in the transport and absorption of zinc. The most common clinical presentation is that seen in breast-fed premature infants. Zinc stores are lower in preterm infants, and their rapid postnatal growth, occurring at a time when maternal breast milk zinc levels are declining, can result in an imbalance between the supply and demand.²⁶²

Rash, irritability, and diarrhea are the most characteristic findings in this form of AE. Focal or confluent erosions are occasionally present. Prominent bullous lesions have been reported and can contribute to diagnostic confusion and a delay

in diagnosis.²⁶³ In addition, acral lesions are often bullous, erosive, or vesicular and can even mimic herpetic whitlow. However, the most characteristic findings are not blisters but rather a periorificial rash (around the mouth and in the perineal area) with fairly distinctive clinical characteristics. In typical cases, sharply demarcated, scaly or honey-crusted plaques are located around the eyes, nose, mouth, anus, and genitalia. Other common sites of involvement are the acral skin, particularly periungual skin, neck folds, and inguinal creases.^{264,265} Irritability and diarrhea are almost always present. The diagnosis is confirmed by low serum zinc levels, although occasional false-positive and false-negative results have been reported.²⁶⁶

The genetic form of AE typically presents later in infancy, often after weaning from breast milk to formula. Alopecia is a more common finding particularly if the condition is not recognized. The cause for the genetic form of AE, *SLC39A4*, has been localized to 8q and is thought to affect a transmembrane protein involved in zinc transport, hZIP4.^{267,268}

Similar findings to AE have been described in a number of other conditions causing metabolic dysregulation or intestinal malabsorption of zinc including cystic fibrosis, biotinidase deficiency, and other metabolic disorders. The term ‘acrodermatitis dysmetabolica’ has been proposed to encompass this diverse group of disorders including AE.²⁶⁹ This condition is discussed in more detail in [Chapter 18](#).

The term ‘methylmalonic acidemia’ (MMA; see [Chapter 17](#)) refers to a group of defects in the metabolism of isoleucine and valine. Skin rashes can result from the metabolic perturbations or the dietary restrictions used to manage these inherited disorders of amino acid metabolism. An erosive erythema with periorificial accentuation resembling staphylococcal scalded skin syndrome and a periorificial rash resembling acrodermatitis enteropathica have both been described in MMA.^{26,270} Other symptoms in early-onset disease include lethargy, hypotonia, neutropenia, and thrombocytopenia. The diagnosis is made by documenting characteristic abnormal levels of plasma amino acids. Treatment with dietary restrictions may be helpful in some cases, and intramuscular hydroxocobalamin is also helpful in some cases.²⁶

EPIDERMOLYTIC HYPERKERATOSIS AND SUPERFICIAL EPIDERMOLYTIC ICHTHYOSIS

Epidermolytic ichthyosis (also known as epidermolytic hyperkeratosis or bullous ichthyosis) is a rare form of ichthyosis which is inherited as an autosomal dominant trait (see [Chapter 19](#)). It is due to mutations in either keratin 1 or 10. At birth, the epidermis is usually thickened, macerated, and erythematous, and bullae or raw denuded areas are present ([Fig. 10.36](#)). In some cases, bullae are a very prominent morphology leading to diagnostic confusion with epidermolysis bullosa.^{271,272} Spontaneous or mechanically induced bullae continue to form throughout infancy and early childhood, especially on the hands and feet, but generalized blistering usually resolves over time. Individuals with the condition are otherwise healthy.^{273,274} Superficial epidermolytic ichthyosis (see also [Chapter 19](#)), previously known as ‘ichthyosis bullosa of Siemens’, is another rare form of ichthyosis, also characterized by blisters and hyperkeratosis, which can easily be confused with epidermolytic ichthyosis. It is due to mutations in Keratin 2e. It can also present in the first months of life and resemble EHK, although blistering is milder and more localized, erythroderma is



Figure 10.36 Epidermolytic ichthyosis presenting with widespread blistering.

typically absent, and there is usually sparing of palms and soles.^{272,275}

RESTRICTIVE DERMOPATHY

Restrictive dermopathy (see [Chapter 19](#)) is a rare autosomal recessive disease characterized by tight, translucent skin, prominent vessels, and skin erosions. These infants are often premature, have multiple joint contractures, a fixed facial expression, micrognathia, microstomia, and more variably blepharophimosis, absent eyelashes, natal teeth, and cardiac defects. There is some heterogeneity to the genetic basis of the condition. Most frequently, recessive mutations of the zinc metalloproteinase ZMPSTE24 gene have been found, or less frequently, by dominant lamin A/C gene mutations.^{276,277} Most infants die in the newborn period.

ULCERATIONS IN VASCULAR ANOMALIES

Ulcerations can be a complication of several types of vascular birthmarks, namely infantile hemangiomas (IH), rapidly involuting congenital hemangiomas and cutis marmorata telangiectatica congenita (see also [Chapters 21](#) and [22](#)). Of these, ulcerations in IH are the most frequent in incidence. Ulcerations are relatively common in IH, developing in approximately 15% of infants referred for dermatology consultation. They occur most often at a few weeks to months of life during the proliferative phase. Certain anatomic sites, particularly intertriginous areas such as the perineum, perioral skin and neck folds are most likely to have ulceration, presumably because friction and moisture can compromise the overlying epidermis. Less commonly, ulceration may actually be the presenting sign of IH, before the diagnosis is obvious.^{278–280} In these cases, there may be an area of port-wine stain-like erythema or blanched skin surrounding the erythema as a so-called ‘hemangioma precursor’. These very early ulcerations are most common on the pinna, the lip, and in the perineal area, but can occur at other sites ([Fig. 10.37](#)).²⁸¹ The presence of an ulceration either superimposed on or in direct contiguity with a vascular lesion is a key clue to the diagnosis.²⁷⁸ [Chapter 21](#) discusses the management of IH ulceration in more detail.

Ulcerations are also occasionally present in fully formed congenital hemangiomas, particularly in the center of rapidly



Figure 10.37 Hemangioma on the buttock presenting as an area of skin ulceration. Note the rim of bright erythema which suggests an evolving hemangioma.

involuting congenital hemangiomas (RICH).²⁸² These ulcerations are often present either at birth or develop soon thereafter. Unlike most ulcerated IH, ulcerations in RICH, though much less common, can result in life-threatening bleeding.

Ulcerations may be present at birth or in early infancy in cutis marmorata telangiectatica congenita (CMTC), a rare vascular anomaly characterized by a coarse livedo-like pattern, often with central atrophy. CMTC is most often located on an extremity but can be more widespread. It can resemble early infantile hemangiomas with central ulceration, but the pattern of telangiectasias is much coarser (see Chapter 22).²⁸³ Severe bleeding is not a usual feature but has been reported in at least one case.²⁸⁴

'BULLAE', ULCERATIONS, AND ABSENT SKIN OVERLYING DEVELOPMENTAL ANOMALIES

Ulcerations or skin lesions resembling bullae can occasionally be present in the skin overlying congenital anomalies or as the presenting manifestation of aplasia cutis congenita (ACC; see Chapter 9). ACC is a clinical finding of absent skin at birth due to a heterogeneous group of causes: hereditary conditions, placental infarction, intrauterine infection, and many other diseases. In most cases, it is easy to distinguish ACC from blistering conditions causing erosions at birth, because the absence of skin in ACC is usually full-thickness, involving both epidermis and dermis, whereas the depth of blisters in most primary blistering disorders it is not as deep.^{285,286}

The scalp is the most common location of ACC. Lesions usually present as raw, ulcerated stellate patches, but one form of ACC, so-called membranous ACC (sometimes called 'bullous ACC') is characterized by sharply demarcated scalp skin defects with a membranous covering. So-called 'membranous ACC' is often fluid-filled, with a palpable depression in the underlying skin (Fig. 10.38A). It is often associated with an increase in hair at the periphery, the 'hair-collar sign'. The location on the scalp, the membranous covering, and the usual concave nature of the underlying defect help distinguish this condition from other forms of blistering. Most are solitary but occasionally multiple lesions are present (Fig. 10.38B). The membranous form of ACC is often a sign of an atretic cephalocele and occasionally has deeper intracranial connections and/or bony defects.²⁸⁷



Figure 10.38 (A) Membranous aplasia cutis: this form of aplasia cutis often has a blister-like appearance. Location at the vertex scalp and the very sharply demarcated oval or circular shape with parchment-like surface are clues to the diagnosis.

Associated vascular stains, large melanocytic nevi, or other skin anomalies may be present.^{288–290}

LINEAR POROKERATOSIS AND POROKERATOTIC ADNEXAL OSTIAL NEVUS

At least two forms of porokeratosis can present with erosions and/or ulcerations in the newborn period: linear porokeratosis and porokeratotic adnexal ostial nevus (PAON), which has also been called porokeratotic eccrine ostial and dermal duct nevus. In both conditions, the pattern is a linear one following the lines of Blaschko.^{291,292} Establishing the diagnosis in the newborn period may be difficult, as initial biopsies can be nondiagnostic, particularly if the erosions rather than scaly areas are biopsied. After the erosions improve and heal, the diagnosis may become more obvious, both clinically and histologically. Infants with both conditions have a risk of eventually developing squamous cell carcinoma in affected skin, but this does not usually happen during childhood (Fig. 10.39).²⁹¹ The differential diagnosis includes Goltz syndrome and intrauterine varicella infection.

EROSIONS AND ULCERATIONS OVERLYING GIANT MELANOCYTIC NEVI

Several cases of erosions or ulcerations overlying giant melanocytic nevi have been reported during the neonatal period.^{293–295}



Figure 10.38 (B) Multiple small bullae as a manifestation of 'bullous' aplasia cutis congenita.



Figure 10.39 Erosions in a newborn with porokeratotic adnexal ostial nevus.

The mechanism of these ulcerations is uncertain, but is possibly due to weakening of the dermoepidermal junction as a result of the large number of melanocytes present together with the stresses of labor and delivery, i.e., perinatal trauma.²⁹⁴ Thus, although ulcerations overlying melanocytic nevi can herald malignant melanoma, the finding does not appear to be as ominous in neonates, although they should have – at a minimum – close follow-up and serial exams. Minor erosions can also be seen in infants and older children with giant nevi, but the finding should be considered more worrisome, particularly if there is no clear-cut history of trauma, and definitely if erosions either persist or become frank ulcerations. In this case, skin biopsy should be strongly considered.^{293–295}

ECTODERMAL DYSPLASIA SYNDROMES

Blistering in the newborn period or early infancy has been reported in several forms of ectodermal dysplasia (ED).

Ankyloblepharon–ectodermal dysplasia–cleft palate (AEC, Hay–Wells syndrome) presents in the newborn period with congenital erythroderma and linear or widespread erosions of the skin.^{296,297} Extensive scalp erosions are reported in 70% of patients and are often present at birth.²⁹⁸ Over the first months of life, a severe erosive dermatitis of the scalp develops, associated with bacterial and fungal infections and resulting in scarring alopecia.^{296,299} Persistent or recurrent erosions elsewhere can also develop and may result in cribriform scarring or atrophy.³⁰⁰ The cutaneous features of AEC have recently been

summarized.³⁰¹ Similar scalp erosions and ulcerations are also a feature of Rapp–Hodgkin ED, which is also due to mutations in p63 (Fig. 10.40).

In focal dermal hypoplasia (Goltz syndrome) blistering is an occasional feature, but the more striking cutaneous features are widespread hypoplasia and aplasia of the skin in linear and whorled patterns following Blaschko's lines. Hair and nail dystrophy are common, as are skeletal and ophthalmologic abnormalities.³⁰²

Basan syndrome (MIM:129200) is characterized by absent dermal ridge patterns, congenital milia, and blisters of the fingertips and soles. Blistering is present at birth and reportedly resembles multiple sucking blisters. Other features of the condition include decreased sweating on the hands and feet, increased heat tolerance, and painful fissures on the fingertips in affected adults.³⁰³

PORPHYRIA

Photosensitive blistering can occur in the newborn period in several forms of porphyria (see also Chapters 8 and 20), including transient porphyrinemia, resulting from hemolytic disease in the newborn period,³⁰⁴ erythropoietic porphyria (Günther disease), and neonatal-onset coproporphyria. Blistering in erythropoietic porphyria can develop within the first few days to weeks of life (Fig. 10.41). Infants usually also have hemolytic anemia.^{305–307} Blisters or erosions may occur on non-inflamed skin in response to visible light, examination lights, as well as other wavelengths contained in natural sunlight. They typically leave some degree of atrophy or scarring. Phototherapy, which may be used to control hyperbilirubinemia either due to porphyria or other causes, can result in generalized, and in some cases severe, blistering.



Figure 10.40 Pustules, erosions, and crusting of the scalp of a 3-week-old with Rapp–Hodgkin ectodermal dysplasia.



Figure 10.41 Congenital erythropoietic porphyria. Bullae, erosions and atrophic scarring – findings which were not present in covered areas that had not been exposed to ultraviolet or visible light.

PERINATAL GANGRENE OF THE BUTTOCK

Perinatal gangrene of the buttock (see [Chapter 8](#)) is a rare condition characterized by the sudden onset of erythema and cyanosis of the buttocks, followed by the progressive development of gangrene and ulcerations. Some cases have been attributed to therapeutic injections via an umbilical artery catheter, but other cases are apparently spontaneous.^{308,309} The distribution of the cutaneous infarction suggests occlusion or spasm of the internal iliac artery.³⁰⁸ The differential diagnosis includes congenital protein C deficiency, and clotting disorders or forms of disseminated intravascular coagulation.

PURPURA FULMINANS

Purpura fulminans can result in blistering due to clotting and ischemic necrosis or impending skin infarction. In the neonatal

period, it is often due to a congenital deficiency of protein S, protein C, or other hypercoagulable states.³¹⁰

Bullae, when present, are typically hemorrhagic. In older infants, purpura fulminans is more often seen as a sequela of infection such as meningococemia rather than inherited coagulation disorders ([Fig. 10.42](#)). Evaluation and management are discussed in [Chapter 20](#).

Access the full reference list at [ExpertConsult.com](#)

Figures 5, 7, 9, 12, 17, 18, 19, 20, 22B, 23, 24, 26, 27, 32, 34, 38B, 39 and 42 are available online at [ExpertConsult.com](#)

KEY REFERENCES

2. Kanada KN, Merin MR, Munden A, et al. A prospective study of cutaneous findings in newborns in the United States: correlation with race, ethnicity, and gestational status using updated classification and nomenclature. *J Pediatr* 2012;161(2):240–5.
5. Antaya RJ, Robinson DM. Blisters and pustules in the newborn. *Pediatr Ann* 2010;39(10):635–45.
6. Hook KP, Eichenfield LF. Approach to the neonate with ecchymoses and crusts. *Dermatol Ther* 2011;24(2):240–8.
7. Mohr MR, Sholtzow M, Bevan HE, et al. Exploring the differential diagnosis of hemorrhagic vesicopustules in a newborn. *Pediatrics* 2011;127(1):e226–e230.
8. James L, Gorwitz RJ, Jones RC, et al. Methicillin-resistant *Staphylococcus aureus* infections among healthy full-term newborns. *Arch Dis Child Fetal Neonatal Ed* 2008;93(1):F40–4.
71. Burgos A, Zaoutis TE, Dvorak CC, et al. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. *Pediatrics* 2008;121(5):e1286–e1294.
82. Marquez L, Levy ML, Munoz FM, et al. A report of three cases and review of intrauterine herpes simplex virus infection. *Pediatr Infect Dis J* 2011;30(2):153–7.
87. Caviness AC, Demmler GJ, Selwyn BJ. Clinical and laboratory features of neonatal herpes simplex virus infection: a case-control study. *Pediatr Infect Dis J* 2008;27(5):425–30.
88. Kimberlin DW, Lin CY, Jacobs RE, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics* 2001;108(2):223–9.
250. McAleer MA, Powell FC, Devaney D, et al. Infantile pyoderma gangrenosum. *J Am Acad Dermatol* 2008;58(2 Suppl):S23–8.



Figure 10.42 Neonatal purpura fulminans. Erosions, blistering, and impending cutaneous infarction as a result of disseminated intravascular coagulation due to congenital hypercoagulability. (Courtesy of Sarah Arron.)

REFERENCES

- Goyal T, Varshney A, Bakshi SK. Incidence of vesicobullous and erosive disorders of neonates: where and how much to worry? Indian J Pediatr 2011; Epub ahead of print.
- Kanada KN, Merin MR, Munden A, et al. A prospective study of cutaneous findings in newborns in the United States: correlation with race, ethnicity, and gestational status using updated classification and nomenclature. J Pediatr 2012;161(2):240–5.
- Peralta L, Rocha G, Morais P, et al. Skin disorders in the neonatal intensive care unit of a central hospital. Eur J Dermatol 2012;22(1):88–92.
- Frieden IJ. The dermatologist in the newborn nursery: Approach to the neonate with blisters, pustules, erosions, and ulcerations. Curr Probl Dermatol 1992;4(4):126–68.
- Antaya RJ, Robinson DM. Blisters and pustules in the newborn. Pediatr Ann 2010;39(10):635–45.
- Hook KP, Eichenfield LF. Approach to the neonate with ecchymoses and crusts. Dermatol Ther 2011;24(2):240–8.
- Mohr MR, Sholtzow M, Bevan HE, et al. Exploring the differential diagnosis of hemorrhagic vesicopustules in a newborn. Pediatrics 2011;127(1):e226–e230.
- James L, Gorwitz RJ, Jones RC, et al. Methicillin-resistant *Staphylococcus aureus* infections among healthy full-term newborns. Arch Dis Child Fetal Neonatal Ed 2008;93(1):F40–4.
- Alsubaie S, Bahkali K, Somily AM, et al. Nosocomial transmission of community-acquired methicillin-resistant *Staphylococcus aureus* in a well-infant nursery of a teaching hospital. Pediatr Int 2012;54(6):786–92.
- Shane AL, Hansen NI, Stoll BJ, et al. Methicillin-resistant and susceptible *Staphylococcus aureus* bacteremia and meningitis in preterm infants. Pediatrics 2012;129(4):e914–e922.
- Hebert AA, Esterly NB. Bacterial and candidal cutaneous infections in the neonate. Dermatol Clin 1986;4(1):3–21.
- Sandhu K, Kanwar AJ. Generalized bullous impetigo in a neonate. Pediatr Dermatol 2004;21(6):667–9.
- Baranwal AK, Singhi SC, Jayashree M. A 5-year PICU experience of disseminated staphylococcal disease, part 2: management, critical care needs and outcome. J Trop Pediatr 2007;53(4):252–8.
- Heath C, Desai N, Silverberg NB. Recent microbiological shifts in perianal bacterial dermatitis: *Staphylococcus aureus* predominance. Pediatr Dermatol 2009;26(6):696–700.
- Lyons M, Vlastarakos PV, Nikolopoulos TP. Congenital and acquired developmental problems of the upper airway in newborns and infants. Early Hum Dev 2012;88(12):951–5.
- Ney AC, English JC 3rd, Greer KE. Coexistent infections on a child's distal phalanx: blistering dactylitis and herpetic whitlow. Cutis 2002;69(1):46–8.
- FRTZayas A, Moustaki M, Tsagris V, et al. MRSA blistering distal dactylitis and review of reported cases. Pediatr Dermatol 2011;28(4):433–5.
- Neylon O, O'Connell NH, Slevin B, et al. Neonatal staphylococcal scalded skin syndrome: clinical and outbreak containment review. Eur J Pediatr 2010;169(12):1503–9.
- Mockenhaupt M, Idzko M, Grosber M, et al. Epidemiology of staphylococcal scalded skin syndrome in Germany. J Invest Dermatol 2005;124(4):700–3.
- Al-Dhalimi MA. Neonatal and infantile erythroderma: a clinical and follow-up study of 42 cases. J Dermatol 2007;34(5):302–7.
- Loughead JL. Congenital staphylococcal scalded skin syndrome: report of a case. Pediatr Infect Dis J 1992;11(5):413–14.
- Lo WT, Wang CC, Chu ML. Intrauterine staphylococcal scalded skin syndrome: report of a case. Pediatr Infect Dis J 2000;19(5):481–2.
- Makhoul IR, Kassis I, Hashman N, et al. Staphylococcal scalded-skin syndrome in a very low birth weight premature infant. Pediatrics 2001;108(1):E16.
- Haveman LM, Fler A, de Vries LS, et al. Congenital staphylococcal scalded skin syndrome in a premature infant. Acta Paediatr 2004;93(12):1661–2.
- Rubenstein AD, Musher DM. Epidemic boric acid poisoning simulating staphylococcal toxic epidermal necrolysis of the newborn infant: Ritter's disease. J Pediatr 1970;77(5):884–7.
- Howard R, Frieden IJ, Crawford D, et al. Methylmalonic acidemia, cobalamin C type, presenting with cutaneous manifestations. Arch Dermatol 1997;133(12):1563–6.
- Honig PJ, Frieden IJ, Kim HJ, et al. Streptococcal intertrigo: an underrecognized condition in children. Pediatrics 2003;112(6 Pt 1):1427–9.
- Spec A, Molero H, Noronha PA. A 3-month-old girl with a rash on her neck and upper chest. Diagnosis: Group A beta-hemolytic (GABHS) *Streptococcus* intertrigo. Pediatr Ann 2009;38(11):607–9.
- Silverman RA, Schwartz RH. Streptococcal intertrigo of the cervical folds in a five-month-old infant. Pediatr Infect Dis J 2012;31(8):872–3.
- Lehtonen OP, Kero P, Ruuskanen O, et al. A nursery outbreak of group A streptococcal infection. J Infect 1987;14(3):263–70.
- Martic J, Mijac V, Jankovic B, et al. Neonatal cellulitis and sepsis caused by group A *Streptococcus*. Pediatr Dermatol 2010;27(5):528–30.
- Lyon M, Doehring MC. Blistering distal dactylitis: a case series in children under nine months of age. J Emerg Med 2004;26(4):421–3.
- Akiyama H, Yamasaki O, Kanzaki H, et al. Streptococci isolated from various skin lesions: the interaction with *Staphylococcus aureus* strains. J Dermatol Sci 1999;19(1):17–22.
- Sugarman JL, Hersch AL, Okamura T, et al. A retrospective review of streptococcal infections in pediatric atopic dermatitis. Pediatr Dermatol 2011;28(3):230–4.
- Lopez JB, Gross P, Boggs TR. Skin lesions in association with beta-hemolytic *Streptococcus* group B. Pediatrics 1976;58(6):859–61.
- Guha A, Eisenhut M, Shears P, et al. Impetigo neonatorum associated with late onset group B streptococcal meningitis. J Infect 2003;47(2):185–7.
- Chakkarapani E, Bill Yoxall C, Morgan C. Facial submandibular cellulitis-adenitis in a preterm infant. Arch Dis Child Fetal Neonatal Ed 2007;92(2):F153.
- Mittal MK, Shah SS, Friedlaender EY. Group B streptococcal cellulitis in infancy. Pediatr Emerg Care 2007;23(5):324–5.
- Evans JR, Allen AC, Stinson DA, et al. Perinatal listeriosis: report of an outbreak. Pediatr Infect Dis 1985;4(3):237–41.
- Gaulin C, Ramsay D, Bekal S. Widespread listeriosis outbreak attributable to pasteurized cheese, which led to extensive cross-contamination affecting cheese retailers, Quebec, Canada, 2008. J Food Prot 2012;75(1):71–8.
- Lorber B. *Listeria monocytogenes*. In: Long SS, editor. Long: Principles and practice of pediatric infectious diseases. 4th ed. Philadelphia: Saunders; 2012. p. 762–6.
- Khuri-Bulos N, McIntosh K. Neonatal *Haemophilus influenzae* infection. Report of eight cases and review of the literature. Am J Dis Child 1975;129(1):57–62.
- Halal F, Delorme L, Brazeau M, et al. Congenital vesicular eruption caused by *Haemophilus influenzae* type b. Pediatrics 1978;62(4):494–6.
- Foca MD. *Pseudomonas aeruginosa* infections in the neonatal intensive care unit. Semin Perinatol 2002;26(5):332–9.
- Boisseau AM, Sarlangue J, Perel Y, et al. Perineal ecthyma gangrenosum in infancy and early childhood: septicemic and nonsepticemic forms. J Am Acad Dermatol 1992;27(3):415–18.
- Duman M, Ozdemir D, Yis U, et al. Multiple erythematous nodules and ecthyma gangrenosum as a manifestation of *Pseudomonas aeruginosa* sepsis in a previously healthy infant. Pediatr Dermatol 2006;23(3):243–6.
- Wu CT, Huang JL. Multiple ecthyma gangrenosum in a healthy infant with community-acquired *Pseudomonas aeruginosa* sepsis. Pediatr Emerg Care 2010;26(10):750–1.
- Pacha O, Hebert AA. Ecthyma gangrenosum and neutropenia in a previously healthy child. Pediatr Dermatol 2012, Epub ahead of print.
- Freeman AF, Mancini AJ, Yogev R. Is noma neonatorum a presentation of ecthyma gangrenosum in the newborn? Pediatr Infect Dis J 2002;21(1):83–5.
- Hughes JR, Newbould M, du Vivier AW, et al. Fatal *Pseudomonas* septicemia and vasculitis in a premature infant. Pediatr Dermatol 1998;15(2):122–4.
- Woods CR. Syphilis in children: congenital and acquired. Semin Pediatr Infect Dis 2005;16(4):245–57.
- Kim JK, Choi SR, Lee HJ, et al. Congenital syphilis presenting with a generalized bullous and pustular eruption in a premature newborn. Ann Dermatol 2011;23(Suppl 1):S127–30.
- Tana M, Lio A, Vento G. Early congenital syphilis in a premature newborn: typical cutaneous manifestations in atypical skin areas. Arch Dis Child Fetal Neonatal Ed 2012;97(6):F471.
- Mallory SB, Krafchik BR. Syphilis. Pediatr Dermatol 1989;6(1):51–2.
- Zhou Q, Wang L, Chen C, et al. A case series of 130 neonates with congenital syphilis: preterm neonates had more clinical evidences of infection than term neonates. Neonatology 2012;102(2):152–6.
- Wu CC, Tsai CN, Wong WR, et al. Early congenital syphilis and erythema multiforme-like bullous targetoid lesions in a 1-day-old newborn: detection of *Treponema pallidum* genomic DNA from the targetoid plaque using nested polymerase chain reaction. J Am Acad Dermatol 2006;55(2 Suppl):S11–15.

57. Benjamin DK Jr, Stoll BJ, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. *Pediatrics* 2010;126(4):e865–e873.
58. Steinbach WJ, Roilides E, Berman D, et al. Results from a prospective, international, epidemiologic study of invasive candidiasis in children and neonates. *Pediatr Infect Dis J* 2012;31(12):1252–7.
59. Darmstadt GL, Dinulos JG, Miller Z. Congenital cutaneous candidiasis: clinical presentation, pathogenesis, and management guidelines. *Pediatrics* 2000;105(2):438–44.
60. Florens A, Maggiolino G, Kamat M, et al. A full-term infant with rash at birth. Congenital cutaneous candidiasis. *Pediatr Ann* 2010;39(9):551–4.
61. Wang SM, Hsu CH, Chang JH. Congenital candidiasis. *Pediatr Neonatol* 2008;49(3):94–6.
62. Chapman RL. *Candida* infections in the neonate. *Curr Opin Pediatr* 2003;15(1):97–102.
63. Leibovitz E. Neonatal candidosis: clinical picture, management controversies and consensus, and new therapeutic options. *J Antimicrob Chemother* 2002;49(Suppl 1):69–73.
64. Cosgrove BF, Reeves K, Mullins D, et al. Congenital cutaneous candidiasis associated with respiratory distress and elevation of liver function tests: a case report and review of the literature. *J Am Acad Dermatol* 1997;37(5 Pt 2):817–23.
65. Tieu KD, Satter EK, Zaleski L, et al. Congenital cutaneous candidiasis in two full-term infants. *Pediatr Dermatol* 2012;29(4):507–10.
66. Baley JE, Kliegman RM, Boxerbaum B, et al. Fungal colonization in the very low birth weight infant. *Pediatrics* 1986;78(2):225–32.
67. Ferrazzini G, Kaiser RR, Hirsig Cheng SK, et al. Microbiological aspects of diaper dermatitis. *Dermatology* 2003;206(2):136–41.
68. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children: recommendations from the CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep* 2009;58(RR-11):1–166.
69. Woodruff CA, Hebert A. Neonatal primary cutaneous aspergillosis: case report and review of the literature. *Pediatr Dermatol* 2002;19(5):439–44.
70. Langan EA, Agarwal RP, Subudhi CP, et al. *Aspergillus fumigatus*: a potentially lethal ubiquitous fungus in extremely low birthweight neonates. *Pediatr Dermatol* 2010;27(4):403–4.
71. Burgos A, Zaoutis TE, Dvorak CC, et al. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. *Pediatrics* 2008;121(5):e1286–e1294.
72. Roth JG, Troy JL, Esterly NB. Multiple cutaneous ulcers in a premature neonate. *Pediatr Dermatol* 1991;8(3):253–5.
73. Etienne KA, Subudhi CP, Chadwick PR, et al. Investigation of a cluster of cutaneous aspergillosis in a neonatal intensive care unit. *J Hosp Infect* 2011;79(4):344–8.
74. Salazar GE, Campbell JR. Trichosporonosis, an unusual fungal infection in neonates. *Pediatr Infect Dis J* 2002;21(2):161–5.
75. Maheshwari A, Stromquist CI, Pereda L, et al. Mixed infection with unusual fungi and staphylococcal species in two extremely premature neonates. *J Perinatol* 2004;24(5):324–6.
76. Linder N, Keller N, Huri C, et al. Primary cutaneous mucormycosis in a premature infant: case report and review of the literature. *Am J Perinatol* 1998;15(1):35–8.
77. Oh D, Notrica D. Primary cutaneous mucormycosis in infants and neonates: case report and review of the literature. *J Pediatr Surg* 2002;37(11):1607–11.
78. Dave SP, Vivero RJ, Roy S. Facial cutaneous mucormycosis in a full-term infant. *Arch Otolaryngol Head Neck Surg* 2008;134(2):206–9.
79. Honig PJ, Brown D. Congenital herpes simplex virus infection initially resembling epidermolysis bullosa. *J Pediatr* 1982;101(6):958–60.
80. Harris HH, Foucar E, Andersen RD, et al. Intrauterine herpes simplex infection resembling mechanobullous disease in a newborn infant. *J Am Acad Dermatol* 1986;15(5 Pt 2):1148–55.
81. Koch LH, Fisher RG, Chen C, et al. Congenital herpes simplex virus infection: two unique cutaneous presentations associated with probable intrauterine transmission. *J Am Acad Dermatol* 2009;60(2):312–15.
82. Marquez L, Levy ML, Munoz FM, et al. A report of three cases and review of intrauterine herpes simplex virus infection. *Pediatr Infect Dis J* 2011;30(2):153–7.
83. Whitley R, Arvin A, Prober C, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *N Engl J Med* 1991;324(7):450–4.
84. Pinninti SG, Angara R, Feja KN, et al. Neonatal herpes disease following maternal antenatal antiviral suppressive therapy: a multicenter case series. *J Pediatr* 2012;161(1):134–8.e1–e3.
85. Elder DE, Minutillo C, Pemberton PJ. Neonatal herpes simplex infection: keys to early diagnosis. *J Paediatr Child Health* 1995;31(4):307–11.
86. Jacobs RF. Neonatal herpes simplex virus infections. *Semin Perinatol* 1998;22(1):64–71.
87. Caviness AC, Demmler GJ, Selwyn BJ. Clinical and laboratory features of neonatal herpes simplex virus infection: a case-control study. *Pediatr Infect Dis J* 2008;27(5):425–30.
88. Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics* 2001;108(2):223–9.
89. Kohl S. Neonatal herpes simplex virus infection. *Clin Perinatol* 1997;24(1):129–50.
90. Kimura H, Futamura M, Ito Y, et al. Relapse of neonatal herpes simplex virus infection. *Arch Dis Child Fetal Neonatal Ed* 2003;88(6):F483–6.
91. Riley LE. Herpes simplex virus. *Semin Perinatol* 1998;22(4):284–92.
92. Berardi A, Lugli L, Rossi C, et al. Neonatal herpes simplex virus. *J Matern Fetal Neonatal Med* 2011;24(Suppl 1):88–90.
93. Paryani SG, Arvin AM. Intrauterine infection with varicella-zoster virus after maternal varicella. *N Engl J Med* 1986;314(24):1542–6.
94. Amir J, Harel L, Smetana Z, et al. The natural history of primary herpes simplex type 1 gingivostomatitis in children. *Pediatr Dermatol* 1999;16(4):259–63.
95. Alkalay AL, Pomerance JJ, Rimoin DL. Fetal varicella syndrome. *J Pediatr* 1987;111(3):320–3.
96. Auriti C, Piersigilli F, De Gasperi MR, et al. Congenital varicella syndrome: still a problem? *Fetal Diagn Ther* 2009;25(2):224–9.
97. Miller E, Cradock-Watson JE, Ridehalgh MK. Outcome in newborn babies given anti-varicella-zoster immunoglobulin after perinatal maternal infection with varicella-zoster virus. *Lancet* 1989;2(8659):371–3.
98. Nathwani D, Maclean A, Conway S, et al. Varicella infections in pregnancy and the newborn. A review prepared for the UK Advisory Group on Chickenpox on behalf of the British Society for the Study of Infection. *J Infect* 1998;36(Suppl 1):59–71.
99. Smith CK, Arvin AM. Varicella in the fetus and newborn. *Semin Fetal Neonatal Med* 2009;14(4):209–17.
100. Brunell PA, Kotchmar GS Jr. Zoster in infancy: failure to maintain virus latency following intrauterine infection. *J Pediatr* 1981;98(1):71–3.
101. Querol I, Bueno M, Cebrian A, et al. Congenital herpes zoster. *Cutis* 1996;58(3):231–4.
102. Mogami S, Muto M, Mogami K, et al. Congenitally acquired herpes zoster infection in a newborn. *Dermatology* 1997;194(3):276–7.
103. Galea SA, Sweet A, Beninger P, et al. The safety profile of varicella vaccine: a 10-year review. *J Infect Dis* 2008;197(Suppl 2):S165–9.
104. Rodriguez-Garcia C, Rodriguez C, Sanchez R, et al. Prevalence of cutaneous findings in Spanish neonates and relationships to obstetric and parental factors. *Pediatr Dermatol* 2012;29(2):232–3.
105. Blatt J, Kastner O, Hodes DS. Cutaneous vesicles in congenital cytomegalovirus infection. *J Pediatr* 1978;92(3):509.
106. Hancox JG, Shetty AK, Sangua OP, et al. Perineal ulcers in an infant: an unusual presentation of postnatal cytomegalovirus infection. *J Am Acad Dermatol* 2006;54(3):536–9.
107. Yasuda K, Sugiura K, Ishikawa R, et al. Perinatal cytomegalovirus-associated bullae in an immunocompetent infant. *Arch Dermatol* 2012;148(6):770–2.
108. Arnon R, Naor N, Davidson S, et al. Fatal outcome of neonatal echovirus 19 infection. *Pediatr Infect Dis J* 1991;10(10):788–9.
109. Mathes EF, Oza V, Frieden IJ, et al. 'Eczema coxsackium' and unusual cutaneous findings in an enterovirus outbreak. *Pediatrics* 2013;132(1):e149–157.
110. Inamadar AC, Palit A, Sampagavi VV, et al. Cutaneous manifestations of Chikungunya fever: observations made during a recent outbreak in south India. *Int J Dermatol* 2008;47(2):154–9.
111. Riyaz N, Riyaz A, Rahima, et al. Cutaneous manifestations of chikungunya during a recent epidemic in Calicut, north Kerala, south India. *Indian J Dermatol Venereol Leprol* 2010;76(6):671–6.
112. Robin S, Ramful D, Zettor J, et al. Severe bullous skin lesions associated with Chikungunya virus infection in small infants. *Eur J Pediatr* 2010;169(1):67–72.
113. Hurwitz S. Scabies in babies. *Am J Dis Child* 1973;126(2):226–8.
114. Ross BG, Wright-McCarthy JK, DeLaMora PA, et al. Transmission of scabies in a newborn nursery. *Infect Control Hosp Epidemiol* 2011;32(5):516–17.
115. Sarkisian EC, Boiko S. Acute localized bullous eruption in a boy. Bullous reaction to insect bites. *Arch Dermatol* 1995;131(11):1329, 1332.

116. Howard R, Frieden IJ. Papular urticaria in children. *Pediatr Dermatol* 1996;13(3):246–9.
117. Gilliam AE, Bruckner AL, Howard RM, et al. Bullous 'cellulitis' with eosinophilia: case report and review of Wells' syndrome in childhood. *Pediatrics* 2005;116(1):e149–e155.
118. Carr JA, Hodgman JE, Freedman RI, et al. Relationship between toxic erythema and infant maturity. *Am J Dis Child* 1966;112(2):129–34.
119. Tarang G, Anupam V. Incidence of vesicobullous and erosive disorders of neonates. *J Dermatol Case Rep* 2011;5(4):58–63.
120. Montegudo B, Labandeira J, Cabanillas M, et al. Prospective study of erythema toxicum neonatorum: epidemiology and predisposing factors. *Pediatr Dermatol* 2012;29(2):166–8.
121. Chang MW, Jiang SB, Orlow SJ. Atypical erythema toxicum neonatorum of delayed onset in a term infant. *Pediatr Dermatol* 1999;16(2):137–41.
122. Luders D. Histologic observations in erythema toxicum neonatorum. *Pediatrics* 1960;26:219–24.
123. Ferrandiz C, Coroleu W, Ribera M, et al. Sterile transient neonatal pustulosis is a precocious form of erythema toxicum neonatorum. *Dermatology* 1992;185(1):18–22.
124. Ramamurthy RS, Reveri M, Esterly NB, et al. Transient neonatal pustular melanosis. *J Pediatr* 1976;88(5):831–5.
125. Chia PS, Leung C, Hsu YL, et al. An infant with transient neonatal pustular melanosis presenting as pustules. *Pediatr Neonatol* 2010;51(6):356–8.
126. Hidano A, Purwoko R, Jitsukawa K. Statistical survey of skin changes in Japanese neonates. *Pediatr Dermatol* 1986;3(2):140–4.
127. Gan VN, Hoang MP. Generalized vesicular eruption in a newborn. *Pediatr Dermatol* 2004;21(2):171–3.
128. Straka BF, Cooper PH, Greer KE. Congenital miliaria crystallina. *Cutis* 1991;47(2):103–6.
129. Ferahbas A, Utas S, Akcakus M, et al. Prevalence of cutaneous findings in hospitalized neonates: a prospective observational study. *Pediatr Dermatol* 2009;26(2):139–42.
130. Mowad CM, McGinley KJ, Foglia A, et al. The role of extracellular polysaccharide substance produced by *Staphylococcus epidermidis* in miliaria. *J Am Acad Dermatol* 1995;33(5 Pt 1):729–33.
131. Sardana K, Mahajan S, Sarkar R, et al. The spectrum of skin disease among Indian children. *Pediatr Dermatol* 2009;26(1):6–13.
132. Murphy WF, Langley AL. Common bullous lesions – presumably self-inflicted – occurring in utero in the newborn infant. *Pediatrics* 1963;32:1099–101.
133. Libow LF, Reinmann JG. Symmetrical erosions in a neonate: a case of neonatal sucking blisters. *Cutis* 1998;62(1):16–17.
134. Montegudo B, Leon-Muinos E. Neonatal sucking blisters. *Indian Pediatr* 2010;47(9):794.
135. Mengesha YM, Hansen RC. Toddler-age nodulocystic acne. *J Pediatr* 1999;134(5):644–8.
136. Bernier V, Weill FX, Hirigoyen V, et al. Skin colonization by *Malassezia* species in neonates: a prospective study and relationship with neonatal cephalic pustulosis. *Arch Dermatol* 2002;138(2):215–18.
137. Rapelanoro R, Mortureux P, Couprie B, et al. Neonatal *Malassezia furfur* pustulosis. *Arch Dermatol* 1996;132(2):190–3.
138. Ayhan M, Sancak B, Karaduman A, et al. Colonization of neonate skin by *Malassezia* species: relationship with neonatal cephalic pustulosis. *J Am Acad Dermatol* 2007;57(6):1012–18.
139. Lane AT, Rehder PA, Helm K. Evaluations of diapers containing absorbent gelling material with conventional disposable diapers in newborn infants. *Am J Dis Child* 1990;144(3):315–18.
140. Ravanfar P, Wallace JS, Pace NC. Diaper dermatitis: a review and update. *Curr Opin Pediatr* 2012;24(4):472–9.
141. Smith WA, Taintor AR, Kos L, et al. Senna-containing laxative inducing blistering dermatitis in toddlers. *Arch Dermatol* 2012;148(3):402–4.
142. Metzker A, Brenner S, Merlob P. Iatrogenic cutaneous injuries in the neonate. *Arch Dermatol* 1999;135(6):697–703.
143. Ashkenazi S, Metzker A, Merlob P, et al. Scalp changes after fetal monitoring. *Arch Dis Child* 1985;60(3):267–9.
144. Cartledge PH, Fox PE, Rutter N. The scars of newborn intensive care. *Early Hum Dev* 1990;21(1):1–10.
145. Mirowski GW, Frieden IJ, Miller C. Iatrogenic scald burn: a consequence of institutional infection control measures. *Pediatrics* 1996;98(5):963–5.
146. Dissanaik S, Wishnew J, Rahimi M, et al. Burns as child abuse: risk factors and legal issues in West Texas and Eastern New Mexico. *J Burn Care Res* 2010;31(1):176–83.
147. Al-Ahdab M, Al-Omawi M. Deep partial scald burn in a neonate: a case report of the first documented domestic neonatal burn. *J Burn Care Res* 2011;32(1):e1–e6.
148. Jarratt M, Ramsdell W. Infantile acropustulosis. *Arch Dermatol* 1979;115(7):834–6.
149. Kahn G, Rywlin AM. Acropustulosis of infancy. *Arch Dermatol* 1979;115(7):831–3.
150. Jennings JL, Burrows WM. Infantile acropustulosis. *J Am Acad Dermatol* 1983;9(5):733–8.
151. Good LM, Good TJ, High WA. Infantile acropustulosis in internationally adopted children. *J Am Acad Dermatol* 2011;65(4):763–71.
152. Vicente J, Espana A, Idoate M, et al. Are eosinophilic pustular folliculitis of infancy and infantile acropustulosis the same entity? *Br J Dermatol* 1996;135(5):807–9.
153. Vignon-Pennamen MD, Wallach D. Infantile acropustulosis. A clinicopathologic study of six cases. *Arch Dermatol* 1986;122(10):1155–60.
154. Falanga V. Infantile acropustulosis with eosinophilia. *J Am Acad Dermatol* 1985;13(5 Pt 1):826–8.
155. Mancini AJ, Frieden IJ, Paller AS. Infantile acropustulosis revisited: history of scabies and response to topical corticosteroids. *Pediatr Dermatol* 1998;15(5):337–41.
156. Hernandez-Martin A, Nuno-Gonzalez A, Colmenero I, et al. Eosinophilic pustular folliculitis of infancy: A series of 15 cases and review of the literature. *J Am Acad Dermatol* 2013;68(1):150–5.
157. Lucky AW, Esterly NB, Heskell N, et al. Eosinophilic pustular folliculitis in infancy. *Pediatr Dermatol* 1984;1(3):202–6.
158. Giard F, Marcoux D, McCuaig C, et al. Eosinophilic pustular folliculitis (Ofuji disease) in childhood: a review of four cases. *Pediatr Dermatol* 1991;8(3):189–93.
159. Larralde M, Rositto A, Giardelli M, et al. Congenital self-healing Langerhans cell histiocytosis: the need for a long term follow up. *Int J Dermatol* 2003;42(3):245–6.
160. Buckley DA, Munn SE, Higgins EM. Neonatal eosinophilic pustular folliculitis. *Clin Exp Dermatol* 2001;26(3):251–5.
161. Patel NP, Laguda B, Roberts NM, et al. Treatment of eosinophilic pustulosis of infancy with topical tacrolimus. *Br J Dermatol* 2012;167(5):1189–91.
162. Siegel DH, Holland K, Phillips RJ, et al. Erosive pustular dermatosis of the scalp after perinatal scalp injury. *Pediatr Dermatol* 2006;23(6):533–6.
163. Shimada R, Masu T, Hanamizu H, et al. Infantile erosive pustular dermatosis of the scalp associated with Klippel-Feil syndrome. *Acta Derm Venereol* 2010;90(2):200–1.
164. Hertz CG, Hambrick GW Jr. Congenital Letterer-Siwe disease. A case treated with vincristine and corticosteroids. *Am J Dis Child* 1968;116(5):553–6.
165. Valderrama E, Kahn LB, Festa R, et al. Benign isolated histiocytosis mimicking chicken pox in a neonate: report of two cases with ultrastructural study. *Pediatr Pathol* 1985;3(1):103–13.
166. Oranje AP, Vuzevski VD, de Groot R, et al. Congenital self-healing non-Langerhans cell histiocytosis. *Eur J Pediatr* 1988;148(1):29–31.
167. Herman LE, Rothman KF, Harawi S, et al. Congenital self-healing reticulohistiocytosis. A new entity in the differential diagnosis of neonatal papulovesicular eruptions. *Arch Dermatol* 1990;126(2):210–12.
168. Morgan EM, Kingsbury DW. Pyridoxal phosphate as a probe of reovirus transcriptase. *Biochemistry* 1980;19(3):484–9.
169. Huang CY, Chao SC, Ho SF, et al. Congenital self-healing reticulohistiocytosis mimicking diffuse neonatal hemangiomatosis. *Dermatology* 2004;208(2):138–41.
170. Kim KJ, Jee MS, Choi JH, et al. Congenital self-healing reticulohistiocytosis presenting as vesicular eruption. *J Dermatol* 2002;29(1):48–9.
171. Inuzuka M, Tomita K, Tokura Y, et al. Congenital self-healing reticulohistiocytosis presenting with hemorrhagic bullae. *J Am Acad Dermatol* 2003;48(5 Suppl):S75–7.
172. Thong HY, Dai YS, Chiu HC. An unusual presentation of congenital self-healing reticulohistiocytosis. *Br J Dermatol* 2003;149(1):191–2.
173. Brazzola P, Schiller P, Kuhne T. Congenital self-healing Langerhans cell histiocytosis with atrophic recovery of the skin: clinical correlation of an immunologic phenomenon. *J Pediatr Hematol Oncol* 2003;25(3):270–3.
174. Jensen ML, Bygum A, Clemmensen O, et al. Congenital self-healing reticulohistiocytosis – an important diagnostic challenge. *Acta Paediatr* 2011;100(5):784–6.
175. Colon-Fontanez F, Eichenfield LE, Krous HF, et al. Congenital Langerhans cell histiocytosis: the utility of the Tzanck test as a diagnostic screening tool. *Arch Dermatol* 1998;134(8):1039–40.
176. Rowden G, Connelly EM, Winkelmann RK. Cutaneous histiocytosis X. The presence of S-100 protein and its use in diagnosis. *Arch Dermatol* 1983;119(7):553–9.
177. Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. *Pediatr Dermatol* 2008;25(3):291–5.
178. Zaenglein AL, Steele MA, Kamino H, et al. Congenital self-healing reticulohistiocytosis

- with eye involvement. *Pediatr Dermatol* 2001;18(2):135–7.
179. Chunharas A, Pabunruang W, Hongeng S. Congenital self-healing Langerhans cell histiocytosis with pulmonary involvement: spontaneous regression. *J Med Assoc Thai* 2002; 85(Suppl 4):S1309–13.
 180. Longaker MA, Frieden IJ, LeBoit PE, et al. Congenital 'self-healing' Langerhans cell histiocytosis: the need for long-term follow-up. *J Am Acad Dermatol* 1994;31(5 Pt 2):910–16.
 181. Bruckner AL. Incontinentia pigmenti: a window to the role of NF-kappaB function. *Semin Cutan Med Surg* 2004;23(2):116–24.
 182. Berlin AL, Paller AS, Chan LS. Incontinentia pigmenti: a review and update on the molecular basis of pathophysiology. *J Am Acad Dermatol* 2002;47(2):169–87; quiz 188–190.
 183. Cohen BA. Incontinentia pigmenti. *Neurol Clin* 1987;5(3):361–77.
 184. Ma HY, Hsieh WS. Disseminated skin manifestations in a neonate with incontinentia pigmenti. *J Pediatr* 2011;159(3):510.
 185. Chang JT, Chiu PC, Chen YY, et al. Multiple clinical manifestations and diagnostic challenges of incontinentia pigmenti – 12 years' experience in 1 medical center. *J Chin Med Assoc* 2008;71(9):455–60.
 186. Fromer ES, Lynch PJ. Neonatal herpes simplex and incontinentia pigmenti. *Pediatr Dermatol* 2001;18(1):86–7.
 187. Stitt WZ, Scott GA, Caserta M, et al. Coexistence of incontinentia pigmenti and neonatal herpes simplex virus infection. *Pediatr Dermatol* 1998;15(2):112–15.
 188. Chu EY, Freeman AE, Jing H, et al. Cutaneous manifestations of DOCK8 deficiency syndrome. *Arch Dermatol* 2012;148(1):79–84.
 189. Chamlin SL, Kao J, Frieden IJ, et al. Ceramide-dominant barrier repair lipids alleviate childhood atopic dermatitis: changes in barrier function provide a sensitive indicator of disease activity. *J Am Acad Dermatol* 2002; 47(2):198–208.
 190. Eberting CL, Davis J, Puck JM, et al. Dermatitis and the newborn rash of hyper-IgE syndrome. *Arch Dermatol* 2004;140(9):1119–25.
 191. Kamei R, Honig PJ. Neonatal Job's syndrome featuring a vesicular eruption. *Pediatr Dermatol* 1988;5(2):75–82.
 192. Burch JM, Weston WL, Rogers M, et al. Cutaneous pustular leukemoid reactions in trisomy 21. *Pediatr Dermatol* 2003;20(3):232–7.
 193. Uhara H, Shiohara M, Baba A, et al. Transient myeloproliferative disorder with vesiculopustular eruption: Early smear is useful for quick diagnosis. *J Am Acad Dermatol* 2009;60(5): 869–71.
 194. Lerner LH, Wiss K, Gellis S, et al. An unusual pustular eruption in an infant with Down syndrome and a congenital leukemoid reaction. *J Am Acad Dermatol* 1996;35(2 Pt 2): 330–3.
 195. Solky BA, Yang FC, Xu X, et al. Transient myeloproliferative disorder causing a vesiculopustular eruption in a phenotypically normal neonate. *Pediatr Dermatol* 2004;21(5):551–4.
 196. Asgari M, Leiferman KM, Piepkorn M, et al. Neonatal eosinophilic pustulosis. *Int J Dermatol* 2006;45(2):131–4.
 197. Ladrigan MK, LeBoit PE, Frieden IJ. Neonatal eosinophilic pustulosis in a 2-month old. *Pediatr Dermatol* 2008;25(1):52–5.
 198. Chang SE, Choi JH, Koh JK. Congenital erythrodermic psoriasis. *Br J Dermatol* 1999;140(3): 538–9.
 199. Liao PB, Robinson R, Howard R, et al. Annular pustular psoriasis – most common form of pustular psoriasis in children: report of three cases and review of the literature. *Pediatr Dermatol* 2002;19(1):19–25.
 200. Minkis K, Aksentijevich I, Goldbach-Mansky R, et al. Interleukin 1 receptor antagonist deficiency presenting as infantile pustulosis mimicking infantile pustular psoriasis. *Arch Dermatol* 2012;148(6):747–52.
 201. Meadows KP, Egan CA, Vanderhooft S. Acute generalized exanthematous pustulosis (AGEP), an uncommon condition in children: case report and review of the literature. *Pediatr Dermatol* 2000;17(5):399–402.
 202. Ersoy S, Paller AS, Mancini AJ. Acute generalized exanthematous pustulosis in children. *Arch Dermatol* 2004;140(9):1172–3.
 203. Kone-Paut I, Gorchakoff-Molinas A, Weschler B, et al. Paediatric Behcet's disease in France. *Ann Rheum Dis* 2002;61(7):655–6.
 204. Lewis MA, Priestley BL. Transient neonatal Behcet's disease. *Arch Dis Child* 1986;61(8): 805–6.
 205. Stark AC, Bhakta B, Chamberlain MA, et al. Life-threatening transient neonatal Behcet's disease. *Br J Rheumatol* 1997;36(6):700–2.
 206. Jog S, Patole S, Koh G, et al. Unusual presentation of neonatal Behcet's disease. *Am J Perinatol* 2001;18(5):287–92.
 207. Lee EH, Kim MR, Kang TW, et al. Diffuse cutaneous mastocytosis with generalized bullae. *Ann Dermatol* 2010;22(1):77–80.
 208. Kleewein K, Lang R, Diem A, et al. Diffuse cutaneous mastocytosis masquerading as epidermolysis bullosa. *Pediatr Dermatol* 2011; 28(6):720–5.
 209. Alvarez-Twose I, Vano-Galvan S, Sanchez-Munoz L, et al. Increased serum baseline tryptase levels and extensive skin involvement are predictors for the severity of mast cell activation episodes in children with mastocytosis. *Allergy* 2012;67(6):813–21.
 210. Oku T, Hashizume H, Yokote R, et al. The familial occurrence of bullous mastocytosis (diffuse cutaneous mastocytosis). *Arch Dermatol* 1990;126(11):1478–84.
 211. Koga H, Kokubo T, Akaishi M, et al. Neonatal onset diffuse cutaneous mastocytosis: a case report and review of the literature. *Pediatr Dermatol* 2011;28(5):542–6.
 212. Storer JS, Galen WK, Nesbitt LT, et al. Neonatal pemphigus vulgaris. *J Am Acad Dermatol* 1982;6(5):929–32.
 213. Bonifazi E, Meneghini CL. Herpes gestationis with transient bullous lesions in the newborn. *Pediatr Dermatol* 1984;1(3):215–18.
 214. Merlob P, Metzker A, Hazaz B, et al. Neonatal pemphigus vulgaris. *Pediatrics* 1986;78(6): 1102–5.
 215. Walker DC, Kolar KA, Hebert AA, et al. Neonatal pemphigus foliaceus. *Arch Dermatol* 1995;131(11):1308–11.
 216. Chen SH, Chopra K, Evans TY, et al. Herpes gestationis in a mother and child. *J Am Acad Dermatol* 1999;40(5 Pt 2):847–9.
 217. Avalos-Diaz E, Olague-Marchan M, Lopez-Swiderski A, et al. Transplacental passage of maternal pemphigus foliaceus autoantibodies induces neonatal pemphigus. *J Am Acad Dermatol* 2000;43(6):1130–4.
 218. Campo-Voegeli A, Muniz F, Mascaro JM, et al. Neonatal pemphigus vulgaris with extensive mucocutaneous lesions from a mother with oral pemphigus vulgaris. *Br J Dermatol* 2002;147(4):801–5.
 219. Hirsch R, Anderson J, Weinberg JM, et al. Neonatal pemphigus foliaceus. *J Am Acad Dermatol* 2003;49(2 Suppl Case Reports):S187–9.
 220. Gushi M, Yamamoto Y, Mine Y, et al. Neonatal pemphigus vulgaris. *J Dermatol* 2008;35(8): 529–35.
 221. Panko J, Florell SR, Hadley J, et al. Neonatal pemphigus in an infant born to a mother with serologic evidence of both pemphigus vulgaris and gestational pemphigoid. *J Am Acad Dermatol* 2009;60(6):1057–62.
 222. Abrams ML, Smidt A, Benjamin L, et al. Congenital epidermolysis bullosa acquisita: vertical transfer of maternal autoantibody from mother to infant. *Arch Dermatol* 2011;147(3): 337–41.
 223. Tope WD, Kamino H, Briggaman RA, et al. Neonatal pemphigus vulgaris in a child born to a woman in remission. *J Am Acad Dermatol* 1993;29(3):480–5.
 224. Crowley E, Frieden IJ. Neonatal lupus erythematosus: an unusual congenital presentation with cutaneous atrophy, erosions, alopecia, and pancytopenia. *Pediatr Dermatol* 1998; 15(1):38–42.
 225. Scheke LE, Kasteler JS, Callen JP. Neonatal lupus erythematosus mimicking langerhans cell histiocytosis. *Pediatr Dermatol* 2003; 20(2):164–6.
 226. Nakajima K, Wakiguchi H, Kodama H, et al. Neonatal lupus erythematosus in identical twins, showing transient bullous lesions. *Pediatr Dermatol* 2011;28(4):397–400.
 227. Inzinger M, Salmhofer W, Binder B. Neonatal lupus erythematosus and its clinical variability. *J Dtsch Dermatol Ges* 2012;10(6):407–11.
 228. Johnston GA, Ghura HS, Carter E, et al. Neonatal erythema multiforme major. *Clin Exp Dermatol* 2002;27(8):661–4.
 229. Scully MC, Frieden IJ. Toxic epidermal necrolysis in early infancy. *J Am Acad Dermatol* 1992;27(2 Pt 2):340–4.
 230. Oranje A, De Groot R. Toxic epidermal necrolysis (TEN) can be considered an extreme and serious form of erythema multiforme. *Pediatr Dermatol* 1985;3(1):83.
 231. Alain G, Carrier C, Beaumier L, et al. In utero acute graft-versus-host disease in a neonate with severe combined immunodeficiency. *J Am Acad Dermatol* 1993;29(5 Pt 2):862–5.
 232. Honig PJ, Gaisin A, Buck BE. Frozen section differentiation of drug-induced and staphylococcal-induced toxic epidermal necrolysis. *J Pediatr* 1978;92(3):504–5.
 233. Ruiz-Maldonado R, Duran-MKinstler C, Carrasco-Daza D, et al. Intrauterine epidermal necrosis: report of three cases. *J Am Acad Dermatol* 1998;38(5 Pt 1):712–15.
 234. Ferrandiz-Pulido C, Garcia-Fernandez D, Dominguez-Sampedro P, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of the experience with paediatric patients in a university hospital. *J Eur Acad Dermatol Venereol* 2011; 25(10):1153–9.
 235. Finkelstein Y, Soon GS, Acuna P, et al. Recurrence and outcomes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *Pediatrics* 2011;128(4):723–8.
 236. Allee JE, Saria EA, Rosenblum D, et al. Intrauterine epidermal necrosis. *J Cutan Pathol* 2001;28(7):383–6.
 237. Cohen BA, Esterly NB, Nelson PF. Congenital erosive and vesicular dermatosis healing with reticulated supple scarring. *Arch Dermatol* 1985;121(3):361–7.

238. Sidhu-Malik NK, Resnick SD, Wilson BB. Congenital erosive and vesicular dermatosis healing with reticulated supple scarring: report of three new cases and review of the literature. *Pediatr Dermatol* 1998;15(3):214–18.
239. Metz BJ, Hicks J, Levy M. Congenital erosive and vesicular dermatosis healing with reticulated supple scarring. *Pediatr Dermatol* 2005;22(1):55–9.
240. Vun YY, Malik MM, Murphy GM, et al. Congenital erosive and vesicular dermatosis. *Clin Exp Dermatol* 2005;30(2):146–8.
241. Goncalves RV, Pessoa OM, Lowy G. Evaluation of a congenital erosive and vesicular dermatosis healing with reticulated supple scarring. *Pediatr Dermatol* 2007;24(4):384–6.
242. De Lange A, Bayet B, Debauche C, et al. Congenital erosive and vesicular dermatosis with reticulated scarring in a newborn: an innovative treatment using a silicone dressing. *Pediatr Dermatol* 2009;26(6):735–8.
243. Stein S, Stone S, Paller AS. Ongoing blistering in a boy with congenital erosive and vesicular dermatosis healing with reticulated supple scarring. *J Am Acad Dermatol* 2001;45(6):946–8.
244. Sadick NS, Shea CR, Schlessel JS. Congenital erosive and vesicular dermatosis with reticulated, supple scarring: a neutrophilic dermatosis. *J Am Acad Dermatol* 1995;32(5 Pt 2):873–7.
245. Nanda A, Alsaleh QA, Al-Sabah H, et al. Lipoid proteinosis: report of four siblings and brief review of the literature. *Pediatr Dermatol* 2001;18(1):21–6.
246. Graham JA, Hansen KK, Rabinowitz LG, et al. Pyoderma gangrenosum in infants and children. *Pediatr Dermatol* 1994;11(1):10–17.
247. Dinulos JG, Darmstadt GL, Len MK, et al. Infantile Crohn disease presenting with diarrhea and pyoderma gangrenosum. *Pediatr Dermatol* 2006;23(1):43–8.
248. Torrelo A, Colmenero I, Serrano C, et al. Pyoderma gangrenosum in an infant. *Pediatr Dermatol* 2006;23(4):338–41.
249. Gumruk F, Tuncer MA, Hicsonmez G. Pyoderma gangrenosum in a child with myelodysplastic syndrome. *J Pediatr Hematol Oncol* 2000;22(4):362–4.
250. McAleer MA, Powell FC, Devaney D, et al. Infantile pyoderma gangrenosum. *J Am Acad Dermatol* 2008;58(2 Suppl):S23–8.
251. Mehta AJ, Charman CR. Pyoderma gangrenosum in association with autoimmune neutropenia of infancy. *Pediatr Dermatol* 2008;25(6):620–2.
252. Yoshida M, Oiso N, Kimura M, et al. Skin ulcer mimicking pyoderma gangrenosum in a patient with incontinentia pigmenti. *J Dermatol* 2011;38(10):1019–21.
253. Rajan N, Das S, Taylor A, et al. Idiopathic infantile pyoderma gangrenosum with stridor responsive to infliximab. *Pediatr Dermatol* 2009;26(1):65–9.
254. Ghosal SP, Sen Gupta PC, Mukherjee AK, et al. Noma neonatorum: Its aetiopathogenesis. *Lancet* 1978;2(8084):289–91.
255. Atiyeh BS, Hashim HA, Rubciz MT, et al. Necrotising infection of the orofacial tissues in neonates (noma neonatorum). Case report. *Scand J Plast Reconstr Surg Hand Surg* 1998;32(3):343–5.
256. Lin JY, Wang DW, Peng CT, et al. Noma neonatorum: an unusual case of noma involving a full-term neonate. *Acta Paediatr* 1992;81(9):720–2.
257. Parikh TB, Nanavati RN, Udani RH. Noma neonatorum. *Indian J Pediatr* 2006;73(5):439–40.
258. Rotbart HA, Levin MJ, Jones JE, et al. Noma in children with severe combined immunodeficiency. *J Pediatr* 1986;109(4):596–600.
259. Goskowitz MO, Friedlander SF, Eichenfield LF. Endemic 'lime' disease: phytophotodermatitis in San Diego County. *Pediatrics* 1994;93(5):828–30.
260. Carlsen K, Weismann K. Phytophotodermatitis in 19 children admitted to hospital and their differential diagnoses: Child abuse and herpes simplex virus infection. *J Am Acad Dermatol* 2007;57(5 Suppl):S88–91.
261. Mill J, Wallis B, Cuttle L, et al. Phytophotodermatitis: case reports of children presenting with blistering after preparing lime juice. *Burns* 2008;34(5):731–3.
262. Chew AL, Chan I, McGrath JA, et al. Infantile acquired zinc deficiency resembling acrodermatitis enteropathica. *Clin Exp Dermatol* 2005;30(5):594–5.
263. Jensen SL, McCuaig C, Zembowicz A, et al. Bullous lesions in acrodermatitis enteropathica delaying diagnosis of zinc deficiency: a report of two cases and review of the literature. *J Cutan Pathol* 2008;35(Suppl 1):1–13.
264. Perafan-Riveros C, Franca LF, Alves AC, et al. Acrodermatitis enteropathica: case report and review of the literature. *Pediatr Dermatol* 2002;19(5):426–31.
265. Kumar V, Aggarwal A, Taneja R, et al. Primary cutaneous mucormycosis in a premature neonate and its management by tumescent skin grafting. *Br J Plast Surg* 2005;58(6):852–4.
266. Van Wouwe JP. Clinical and laboratory diagnosis of acrodermatitis enteropathica. *Eur J Pediatr* 1989;149(1):2–8.
267. Nakano A, Nakano H, Nomura K, et al. Novel SLC39A4 mutations in acrodermatitis enteropathica. *J Invest Dermatol* 2003;120(6):963–6.
268. Wang F, Kim BE, Dufner-Beattie J, et al. Acrodermatitis enteropathica mutations affect transport activity, localization and zinc-responsive trafficking of the mouse ZIP4 zinc transporter. *Hum Mol Genet* 2004;13(5):563–71.
269. Tabanlıoğlu D, Ersoy-Evans S, Karaduman A. Acrodermatitis enteropathica-like eruption in metabolic disorders: acrodermatitis dysmetabolica is proposed as a better term. *Pediatr Dermatol* 2009;26(2):150–4.
270. Bodemer C, De Prost Y, Bachollet B, et al. Cutaneous manifestations of methylmalonic and propionic acidemia: a description based on 38 cases. *Br J Dermatol* 1994;131(1):93–8.
271. Klein I, Bergman R, Indelman M, et al. A newborn presenting with congenital blistering. *Int J Dermatol* 2004;43(4):295–7.
272. Oji V, Tadini G, Akiyama M, et al. Revised nomenclature and classification of inherited ichthyoses: results of the First Ichthyosis Consensus Conference in Soreze 2009. *J Am Acad Dermatol* 2010;63(4):607–41.
273. Traupe H, Kolde G, Hamm H, et al. Ichthyosis bullosa of Siemens: a unique type of epidermolytic hyperkeratosis. *J Am Acad Dermatol* 1986;14(6):1000–5.
274. Ammirati CT, Mallory SB. The major inherited disorders of cornification. *New advances in pathogenesis. Dermatol Clin* 1998;16(3):497–508.
275. Cervantes T, Pham C, Browning JC. Superficial epidermolytic ichthyosis: a report of two families. *Pediatr Dermatol* 2013;30(4):469–72.
276. Yesil G, Hatipoglu L, Esteves-Vieira V, et al. Restrictive dermopathy in a Turkish newborn. *Pediatr Dermatol* 2011;28(4):408–11.
277. Ahmad Z, Phadke SR, Arch E, et al. Homozygous null mutations in ZMPSTE24 in restrictive dermopathy: evidence of genetic heterogeneity. *Clin Genet* 2012;81(2):158–64.
278. Liang MG, Frieden IJ. Perineal and lip ulcerations as the presenting manifestation of hemangioma of infancy. *Pediatrics* 1997;99(2):256–9.
279. Knispel J, Shaw JC. Nonhealing perianal ulcer. *Arch Dermatol* 2001;137(3):365–70.
280. Abid N, Rashid A. Haemangioma presenting as perianal ulcer in neonates. *J Perinatol* 2004;24(5):327–8.
281. Kim HJ, Colombo M, Frieden IJ. Ulcerated hemangiomas: clinical characteristics and response to therapy. *J Am Acad Dermatol* 2001;44(6):962–72.
282. Boon LM, Enjolras O, Mulliken JB. Congenital hemangioma: evidence of accelerated involution. *J Pediatr* 1996;128(3):329–35.
283. Kienast AK, Hoeger PH. Cutis marmorata telangiectatica congenita: a prospective study of 27 cases and review of the literature with proposal of diagnostic criteria. *Clin Exp Dermatol* 2009;34(3):319–23.
284. Hu JJ, Chen MT, Tai HC, et al. Cutis marmorata telangiectatica congenita with gangrenous ulceration and hypovolaemic shock. *Eur J Pediatr* 2005;164(7):411–13.
285. Frieden IJ. Aplasia cutis congenita: a clinical review and proposal for classification. *J Am Acad Dermatol* 1986;14(4):646–60.
286. Baselga E, Torrelo A, Drolet BA, et al. Familial nonmembranous aplasia cutis of the scalp. *Pediatr Dermatol* 2005;22(3):213–17.
287. Drolet B, Prendiville J, Golden J, et al. 'Membranous aplasia cutis' with hair collars. Congenital absence of skin or neuroectodermal defect? *Arch Dermatol* 1995;131(12):1427–31.
288. Fujita Y, Yokota K, Akiyama M, et al. Two cases of atypical membranous aplasia cutis with hair collar sign: one with dermal melanocytosis, and the other with naevus flammeus. *Clin Exp Dermatol* 2005;30(5):497–9.
289. Herron MD, Coffin CM, Vanderhooft SL. Vascular stains and hair collar sign associated with congenital anomalies of the scalp. *Pediatr Dermatol* 2005;22(3):200–5.
290. Lam J, Dohil MA, Eichenfield LF, et al. SCALP syndrome: sebaceous nevus syndrome, CNS malformations, aplasia cutis congenita, limbal dermoid, and pigmented nevus (giant congenital melanocytic nevus) with neurocutaneous melanosis: a distinct syndromic entity. *J Am Acad Dermatol* 2008;58(5):884–8.
291. Fisher CA, LeBoit PE, Frieden IJ. Linear porokeratosis presenting as erosions in the newborn period. *Pediatr Dermatol* 1995;12(4):318–22.
292. Goddard DS, Rogers M, Frieden IJ, et al. Widespread porokeratotic adnexal ostial nevus: clinical features and proposal of a new name unifying porokeratotic eccrine ostial and dermal duct nevus and porokeratotic eccrine and hair follicle nevus. *J Am Acad Dermatol* 2009;61(6):1060.e1–1060.14.

293. Giam YC, Williams ML, Leboit PE, et al. Neonatal erosions and ulcerations in giant congenital melanocytic nevi. *Pediatr Dermatol* 1999;16(5):354–8.
294. Borbujo J, Jara M, Cortes L, et al. A newborn with nodular ulcerated lesion on a giant congenital nevus. *Pediatr Dermatol* 2000;17(4):299–301.
295. Gonzalez J, Palangio M, Fialkoff CN, et al. Giant congenital melanocytic nevus with a large ulceration at birth: a 5-year follow-up. *J Am Acad Dermatol* 2003;49(4):752–4.
296. Vanderhooft SL, Stephan MJ, Sybert VP. Severe skin erosions and scalp infections in AEC syndrome. *Pediatr Dermatol* 1993;10(4):334–40.
297. Sawardekar SS, Zaenglein AL. Ankyloblepharon-ectodermal dysplasia-clefting syndrome: a novel p63 mutation associated with generalized neonatal erosions. *Pediatr Dermatol* 2011;28(3):313–17.
298. Siegfried E, Bree A, Fete M, et al. Skin erosions and wound healing in ankyloblepharon-ectodermal defect-cleft lip and/or palate. *Arch Dermatol* 2005;141(12):1591–4.
299. Steele JA, Hansen H, Arn P, et al. Spectrum of phenotypic manifestations from a single point mutation of the p63 gene, including new cutaneous and immunologic findings. *Pediatr Dermatol* 2005;22(5):415–19.
300. Hill VA, Nischal KK, Collin JR, et al. An unusual ectodermal dysplasia with unique eye defects. *Br J Dermatol* 2005;152(2):365–7.
301. Julapalli MR, Scher RK, Sybert VP, et al. Dermatologic findings of ankyloblepharon-ectodermal defects-cleft lip/palate (AEC) syndrome. *Am J Med Genet A* 2009;149A(9):1900–6.
302. Goltz RW, Henderson RR, Hitch JM, et al. Focal dermal hypoplasia syndrome. A review of the literature and report of two cases. *Arch Dermatol* 1970;101(1):1–11.
303. Reed T, Schreiner RL. Absence of dermal ridge patterns: genetic heterogeneity. *Am J Med Genet* 1983;16(1):81–8.
304. Mallon E, Wojnarowska F, Hope P, et al. Neonatal bullous eruption as a result of transient porphyrinemia in a premature infant with hemolytic disease of the newborn. *J Am Acad Dermatol* 1995;33(2 Pt 2):333–6.
305. Takeuchi H, Kondo M, Daimon M, et al. Neonatal-onset hereditary coproporphyria with male pseudohermaphroditism. *Blood* 2001;98(13):3871–3.
306. Lazebnik N, Lazebnik RS. The prenatal presentation of congenital erythropoietic porphyria: report of two siblings with elevated maternal serum alpha-fetoprotein. *Prenat Diagn* 2004;24(4):282–6.
307. Hogeling M, Fardin SR, Frieden IJ, et al. Forehead pressure necrosis in neonates following continuous positive airway pressure. *Pediatr Dermatol* 2012;29(1):45–8.
308. Bonifazi E, Meneghini C. Perinatal gangrene of the buttock: an iatrogenic or spontaneous condition? *J Am Acad Dermatol* 1980;3(6):596–8.
309. Serrano G, Aliaga A, Febrer I, et al. Perinatal gangrene of the buttock: a spontaneous condition. *Arch Dermatol* 1985;121(1):23–4.
310. Price VE, Ledingham DL, Krumpel A, et al. Diagnosis and management of neonatal purpura fulminans. *Semin Fetal Neonatal Med* 2011;16(6):318–22.

Inherited and Acquired Blistering Diseases

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Inherited blistering diseases

EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa (EB) is a family of rare, inherited disorders characterized by fragility of the skin and sometimes the mucosa in response to minor mechanical trauma. EB is caused by mutations in at least 14 genes^{1,2} that encode proteins of the basement membrane zone (BMZ) of the skin (Fig. 11.1). BMZ proteins are structural molecules involved in the adhesion of the epidermis and dermis. When an affected protein is absent or abnormal, adhesion strength is diminished and blistering occurs as a response to frictional stress. Data from the National Epidermolysis Bullosa Registry (NEBR) estimates the incidence of all forms of EB in the USA to be 20 cases/million live births.³

The classification of EB was revised in 2008 and utilizes the level of ultrastructural blistering as the primary categorical designation.¹ The four major types of EB are: EB simplex (EBS) where cleavage occurs in the epidermis; junctional EB (JEB) with blistering through the BMZ; dystrophic EB (DEB) with cleavage arising in the superficial dermis, and Kindler syndrome where multiple splits can be seen. Each type is further divided into major and minor subtypes based on inheritance pattern, clinical findings, and the implicated molecular and genetic defects (Table 11.1).

Clinical features of epidermolysis bullosa

Friction-induced blisters and erosions are the cardinal cutaneous features of EB. The distribution and extent of blistering varies depending on the disease subtype. Some forms of EB, such as EBS and dominant DEB (DDEB), are stereotyped as mild and often localized, whereas blistering in recessive DEB (RDEB) and JEB is often severe and generalized. It is important to remember that these generalizations best apply to older infants and children in whom a 'mature' EB phenotype has developed. In contrast, neonates with any type of EB may present with widespread cutaneous blistering and erosions. Mucosal erosions and absent or dystrophic nails can also be seen in neonates with all forms of EB. Thus, diagnosing the specific type and subtype based on clinical findings alone can be difficult in the first weeks of life, and biopsies are indicated (see below). Certain EB subtypes are associated with extracutaneous manifestations and complications that can begin to present in infancy and early childhood.

NEONATAL FEATURES

Neonates with EB may present at birth with large ulcers, usually on the lower extremities, called congenital localized absence of

skin (CLAS) (Fig. 11.2). The edges of such ulcers are well-demarcated and the base is red and shiny. Bart and colleagues⁴ originally described the association of CLAS, mucosal blistering, and nail dystrophy and proposed that this triad represented a distinct syndrome, later termed Bart syndrome. Since that description, however, CLAS has been reported as a presenting sign in all types of EB, and Bart's original kindred was further examined and found to have DDEB.⁵ CLAS likely results from intrauterine friction, such as the leg rubbing against the uterine wall, and is not specific for any one type of EB. The use of the term Bart syndrome is now discouraged.

With or without CLAS, neonates with EB develop friction-induced blistering and erosions after birth. Skin changes may initially correlate with areas traumatized during birthing, such as the scalp and face in cases of vaginal birth. In many instances, blistering may be generalized. After birth, areas that are most subject to friction, such as the hands, diaper area, extensor extremities, and back, are most likely to blister (Fig. 11.3). Intact blisters are filled with serous or hemorrhagic fluid. In JEB and RDEB, the bullae can be quite large, and the pressure of fluid within the blister cavity can cause the lesion to extend (Fig. 11.4). More superficial blisters may rupture easily, leaving open erosions.

The blisters in EBS and JEB often heal without scarring, but macular hypo- or hyperpigmentation may be a transient change after blisters heal. DEB blisters heal with scarring that is often atrophic. Milia are most suggestive of DEB but can be seen in all forms of EB (Fig. 11.5). Granulation tissue, which is often described as 'exuberant' or 'hyper-' in JEB, can be seen in any EB erosion that has been slow to heal but is not often seen in the neonatal period.

Oral involvement is most often seen in neonates with JEB or DEB but can be seen in EBS as well. Open erosions or intact vesicles can occur on the lips, gums, and palate. These lesions probably result from the trauma of sucking and may result in pain with feeding. In any form of EB, trauma to the periungual skin can result in nails that are absent, dystrophic, or may be shed.

Blisters and erosions are at risk of becoming infected, signaled by the formation of crusts and foul-smelling or purulent drainage. Neonates with EB and extensive erosions are at risk for developing fluid and electrolyte abnormalities as well as sepsis. Neonates with EB and pyloric atresia may present with gastrointestinal obstruction at birth.⁶ In these cases, polyhydramnios and gastric distension may have been noted on prenatal ultrasound, and genitourinary strictures and obstruction may be present as well. Airway involvement is uncommon in neonates with EB, but can occur. Although it is most often associated with JEB-Herlitz (JEB-H), laryngeal involvement can occur in infants with certain forms of EBS and with RDEB.⁷ An

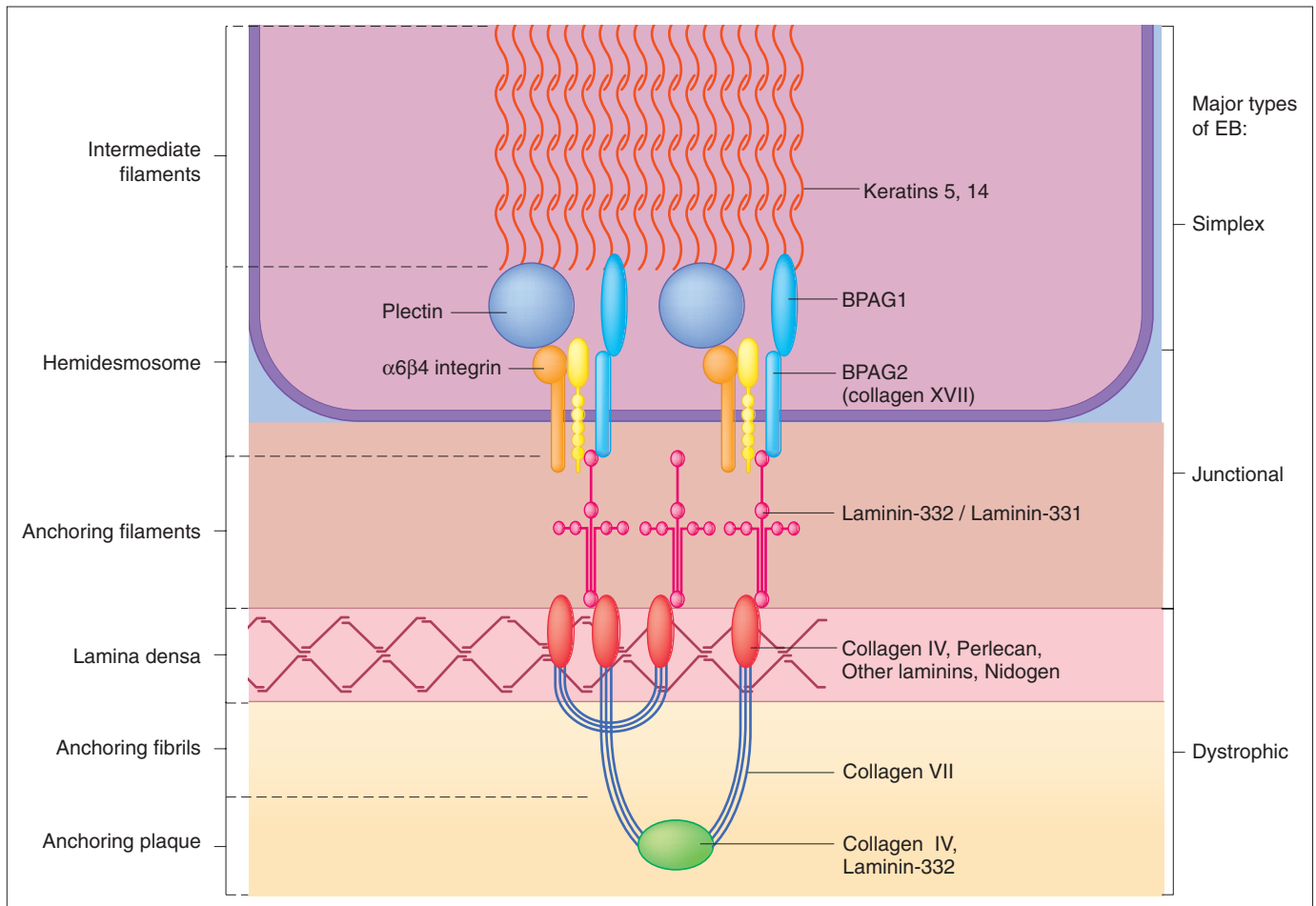


Figure 11.1 Many proteins interact to form the basement membrane zone, the junction of the epidermis and dermis. (Courtesy of Dr M. Peter Marinkovich.)

early sign of blisters and erosions of the larynx is hoarseness, which can progress to stridor as airway obstruction worsens.

Specific epidermolysis bullosa subtypes

SUPRABASAL EPIDERMOLYSIS BULLOSA SIMPLEX

Lethal acantholytic EB (LAEB) is an extremely rare subtype of EB.^{8–10} Affected infants present at birth with rapidly progressive erosions with a positive Nikolsky's sign. Intact vesicles and erosions are not seen. Other common features are complete alopecia, anonychia, and oral erosions. All reported cases have been fatal in the neonatal period. Histology shows suprabasal acantholysis, but immunofluorescence studies will be negative for pemphigus and the typical causes of EB (see below). Ultrastructural studies show that keratin filaments fail to connect properly to desmosomes. Loss of function mutations in *DSP* that lead to truncation of the desmoplakin protein are causative.

Plakophilin deficiency was initially described in 1997 as ectodermal dysplasia/skin fragility syndrome, by McGrath and colleagues.¹¹ Children with this disorder develop spontaneous erosions and fissures, and the perioral area is commonly affected. Painful, fissured keratoderma, absent, sparse or wooly hair, nail dystrophy, and growth failure are other universal features.¹²

Biopsies of affected skin show acanthosis and hyperkeratosis and widened spaces between keratinocytes in the spinous layer. Desmosomes are small and poorly formed on electron microscopy. This is an autosomal recessive disorder caused by mutations in the *PKP1* gene that encodes plakophilin.

BASAL EPIDERMOLYSIS BULLOSA SIMPLEX

Basal EBS is the most common and often mildest form of EB. Most forms are transmitted in an autosomal dominant manner. Individuals with localized forms of EBS may not present for medical evaluation, thus precise estimates of the true prevalence of EBS are lacking. For example, the NEBR calculated the prevalence of EBS to be 4.60 cases/million, but also estimated that the registry probably captured only 10% of all individuals affected with EBS.³ Population-based data from Scotland show a prevalence of 28.6 cases/million in 1992.¹³

EBS, localized (EBS-loc, formerly Weber–Cockayne) is characterized by blisters of the hands and feet. Other than mild oral disease, extracutaneous involvement does not occur. Patients may first develop blisters at any age, including birth, but it is common for the first signs to present in the toddler years, or sometimes as late as adolescence, after a period of marked frictional stress.

EBS, other generalized (EBS, gen-nonDM, formerly Koebner) presents at birth and is characterized by intraepidermal

TABLE
11.1

The classification of epidermolysis bullosa

Major EB type	Major subtype	Minor subtype	Affected gene(s) (protein)	Typical inheritance
Simplex	Suprabasal	Lethal acantholytic EB	<i>DSP</i> (desmoplakin)	AR
		Plakophilin deficiency (ectodermal dysplasia with skin fragility)	<i>PKP1</i> (plakophilin)	AR
		EBS superficialis	?	?
	Basal	Localized (formerly Weber–Cockayne)	<i>KRT5</i> (keratin 5), <i>KRT14</i> (keratin 14)	AD
		Dowling–Meara	<i>KRT5</i> (keratin 5), <i>KRT14</i> (keratin 14)	AD
		Other generalized (formerly Koebner)	<i>KRT5</i> (keratin 5), <i>KRT14</i> (keratin 14)	AD
		With mottled pigmentation	<i>KRT5</i> (keratin 5)	AD
		With muscular dystrophy	<i>PLEC1</i> (plectin)	AR
		With pyloric atresia	<i>PLEC1</i> (plectin), <i>ITGA6</i> , <i>ITGB4</i> ($\alpha 6\beta 4$ integrin)	AR
		Autosomal recessive	<i>KRT14</i> (keratin 14)	AR
		Ogna	<i>PLEC1</i> (plectin)	AD
		Migratory circinate	<i>KRT5</i> (keratin 5)	AD
Junctional	Herlitz	–	<i>LAMA3</i> , <i>LAMB3</i> , <i>LAMC2</i> (laminin-332*)	AR
	Other	Non-Herlitz, generalized	<i>LAMA3</i> , <i>LAMB3</i> , <i>LAMC2</i> (laminin-332*), <i>COL17A1</i> (type XVII collagen)	AR
		Non-Herlitz, localized	<i>COL17A1</i> (type XVII collagen)	AR
		With pyloric atresia	<i>ITGA6</i> , <i>ITGB4</i> ($\alpha 6\beta 4$ integrin)	AR
		Inversa	<i>LAMA3</i> , <i>LAMB3</i> , <i>LAMC2</i> (laminin-332*)	AR
		Late onset LOC syndrome (Shabbir syndrome)	<i>COL17A1</i> (type XVII collagen) <i>LAMA3</i> (laminin-332* α chain)	AR AR
Dystrophic	Dominant	Generalized	<i>COL7A1</i> (type VII collagen)	AD
		Acral		
		Pretibial		
		Pruriginosa		
		Nails only		
		Bullous dermolysis of the newborn		
	Recessive	Severe generalized (former Hallopeau–Siemens) Generalized other (formerly non-Hallopeau–Siemens) Inversa Pretibial Pruriginosa Centripetalis Bullous dermolysis of the newborn	<i>COL7A1</i> (type VII collagen)	AR
Kindler syndrome	–	–	<i>FERMT1</i> (kindlin-1)	AR

AD, autosomal dominant; AR, autosomal recessive; LOC, laryngo-onycho-cutaneous; *Laminin-332 was formerly called laminin-5.

blistering in a generalized distribution. Oral involvement can be seen in infancy but improves with age. Atrophic scarring, dyspigmentation, and nail dystrophy may be seen. Extracutaneous involvement in this type of EB is uncommon. For both EBS-loc and EBS, gen-nonDM, life expectancy is normal and the overall prognosis is good. However, affected adults report that acral blistering can be painful and limits daily activities such as walking, thereby affecting quality of life.^{14,15}

EBS Dowling–Meara (EBS-DM), on the other hand, is more severe and can even be fatal in the newborn period.^{14,16,17} Blistering presents at birth or within the first days of life. Skin involvement ranges from generalized to localization of blisters and erosions to areas of friction. A clinical clue to the diagnosis of EBS-DM is the occurrence of blisters in grouped or annular configurations (Fig. 11.6). This feature, however, is not always reliable and may not be present until after 1 year of age. Milia

and atrophic scarring may occur, and nail dystrophy in which nails may be thickened, ridged, or shed, is fairly common. In childhood, a confluent palmoplantar keratoderma develops and becomes more prominent with age, persisting into adulthood. This hyperkeratosis can interfere with ambulation, and joint contractures may be a subsequent complication.^{14,17} Oral blistering is often present and varies in severity. Laryngeal involvement, presenting as hoarseness, has been reported, but unlike in JEB, does not signal a poor prognosis.¹⁸ Gastroesophageal reflux and constipation may also be seen as complications.¹⁹ The severity of EBS-DM generally improves over time, with less blistering in adolescence, and rare blistering in adulthood in many cases. Patients may also report reduced blistering during febrile illnesses.

EBS with mottled pigmentation (EBS-MP) is a rare subtype.²⁰ It is characterized by acral, nonscarring blistering that presents



Figure 11.2 Congenital localized absence of skin can be seen in all types of EB.



Figure 11.3 Blistering caused by the edge of a diaper in an infant with a milder form of EB.

in infancy. In addition, 2–5 mm hypo- and hyperpigmented macules occur in a reticulate pattern around the neck, axillary, and groin areas. This mottled pigmentation may be congenital or can develop later in infancy.

EBS with muscular dystrophy (EBS-MD), EBS with pyloric atresia (EBS-PA), and EBS, Ogna (EBS-Og) are all due to mutations in *PLEC1*, encoding plectin, although EBS-MD and EBS-PA are inherited recessively and EBS-Og is autosomal dominant.²¹ EBS-MD is a rare disorder that begins at or shortly after birth with mild generalized blistering and mucous membrane involvement. Other cutaneous findings include milia, atrophic scarring, and nail dystrophy.²² Nonmucosal findings can include respiratory involvement and dental



Figure 11.4 Tense, fluid-filled blisters rapidly enlarge in patients with severe EB phenotypes.



Figure 11.5 Healing with milia most often occurs in DEB.



Figure 11.6 Annular blistering is characteristic of EBS-MD.

enamel hypoplasia, leading to prominent caries. In most cases, progressive muscle weakness begins in adolescence or adulthood, although onset in infancy has been reported.²³ The presentation of neonates with EB with pyloric atresia is discussed below.

Genetics and pathogenesis

EBS-DM, EBS-loc, and EBS, gen-nonDM are dominantly inherited, and mutations in *KRT5* and *KRT14* can be identified in about 75% of cases.²⁴ Keratin-5 and -14 are complementary intermediate filaments expressed in basal keratinocytes. They are crucial components of the cytoskeleton involved in maintaining structural integrity. In addition, they function in the adhesion of these cells to the BMZ by attaching to the hemidesmosome via plectin (see Fig. 11.1).²⁵ Mutations in these keratin genes lead to abnormal keratin intermediate filaments with reduced ability to withstand frictional stress, resulting in basal cell cytolysis histologically and in blistering clinically. Genotype–phenotype correlations for mutations *KRT5* and *KRT14* suggest that alterations in the highly conserved boundary domains of the α -helical rod domain lead to the Dowling–Meara phenotype, whereas mutations in the less conserved regions produce milder phenotypes.²⁴

Most cases of EBS-MP are due to a specific point mutation in the nonhelical amino-terminal head domain of keratin-5,²⁶ although a case with a mutation in *KRT14* has been reported.²⁷ Exactly how these mutations lead to disruption of keratin intermediate filaments or pigmentation is unclear.

Plectin, the affected protein in EBS-MD, EBS-PA, and EBS-Og anchors basal keratins to the hemidesmosome and is also expressed in the sarcolemma of muscle. The EBS-MD phenotype tends to correlate with mutations affecting the central rod domain of plectin, while EBS-PA is due to mutations outside this domain.²⁸ The Ogna phenotype is due to a heterozygous missense mutation exerting a dominant negative effect.

JUNCTIONAL EPIDERMOLYSIS BULLOSA

Junctional epidermolysis bullosa (JEB) is the least common type of EB. Data from the NEBR suggests an incidence of two cases/million live births.³ Inheritance of all forms of JEB is autosomal recessive, and a spectrum of clinical phenotypes can be seen. The JEB–Herlitz (JEB-H) and JEB with pyloric atresia

(JEB-PA) subtypes, however, are often incompatible with survival beyond infancy.

JEB-H is characterized by generalized skin and mucosal erosions with a propensity for wounds to form exuberant granulation tissue. Other associated findings include nail dystrophy (Fig. 11.7), dental enamel hypoplasia, and involvement of the respiratory epithelium. Blistering and erosions are seen at, or shortly after, birth (Fig. 11.8A), although the amount of blistering is not predictive of outcome, as infants with little skin involvement can do poorly. Severe involvement of the back and buttocks is common but not pathognomonic (Fig. 11.8B). In neonates who survive into infancy, the development of exuberant or hypergranulation tissue within erosions is a finding with high specificity for JEB-H. The central face, especially the periorificial areas (Fig. 11.9), periungual skin (paronychia inflammation), and nape of the neck are commonly affected. Absent or dystrophic nails or nail shedding are often present. Ocular erosions can also occur.⁷ Oral blistering and erosions are often present in the neonatal period and can make feeding difficult. The laryngeal and respiratory epithelia may also be affected, typically first presenting as a weak or hoarse cry.²⁹ Stridor suggests worsening airway obstruction, which can be fatal. Involvement of the gastrointestinal and urinary epithelia can also occur. Anemia, probably due to a combination of iron



Figure 11.7 Junctional EB. Nail dystrophy at birth. (Courtesy of Dr Julie S. Prendiville.)

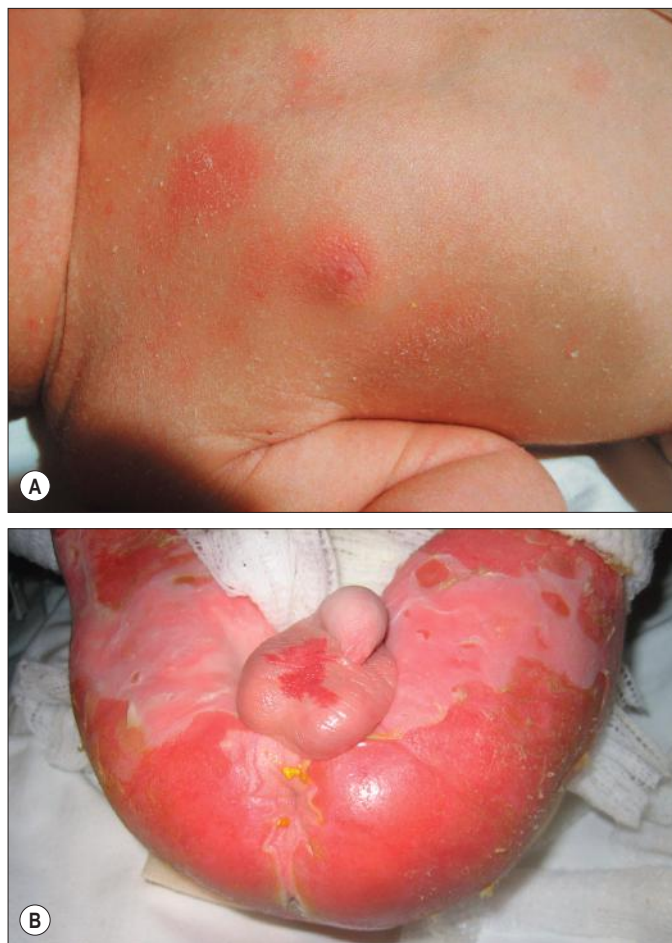


Figure 11.8 (A) Junctional EB infant at 2 h of age; localized erythema and erosions. (B) Same infant 1 week later with diffuse erosions.



Figure 11.9 Exuberant granulation tissue in a nonhealing facial erosion in a toddler with JEB-H. A tracheostomy tube is also in place.

deficiency and chronic inflammation, is common. Patients with JEB-H typically die in the first few years of life due to failure to thrive, sepsis, pneumonia or respiratory failure. Data from the NEBR reported a cumulative risk of death of ~45% in the first year of life,³⁰ while the Dutch EB registry found that over 23 years, all 22 subjects with JEB-H passed away in the first 3 years, with the average age of death being 5.8 months.³¹

JEB-non-Herlitz, generalized (JEB-nH gen) has features similar to JEB-H, although it is generally less severe and its overall prognosis tends to be better.³² In the neonatal period, however, clinical signs and pathologic analysis may not fully distinguish between JEB-H and JEB-nH gen, and a final diagnosis may be based on long-term outcome and/or results of genetic mutation analysis. Generalized blistering and mucous membrane involvement are seen in the neonatal period, and both improve as the child ages. Healing with granulation tissue is less common and less pronounced than in JEB-H, but can occur. Cutaneous lesions may heal with atrophy and pigmentary alterations. In hair-bearing areas, progressive alopecia may result, although this finding is most pronounced in adulthood. Likewise, nail dystrophy can begin in infancy and is progressive and marked with increasing age. Laryngeal involvement may occur, sometimes resulting in respiratory failure. Although the overall prognosis for JEB-nH gen is generally better than for JEB-H, the fatalities in the neonatal period and infancy are not uncommon. Data from the NEBR reported a cumulative risk of death of 40% and 49% in the first year and 2 years of life, respectively.³⁰

EB with pyloric atresia (EBS-PA or JEB-PA) presents at birth with upper gastrointestinal obstruction, most often affecting the pylorus. The degree of skin involvement is variable and ranges from extensive CLAS to normal skin, with the onset of blistering at several months of age.³³ Prenatal signs of an affected fetus include polyhydramnios and abdominal masses appreciated on ultrasound.³⁴ The ocular, respiratory, and urogenital epithelia are often affected. The prognosis for neonates with EB with pyloric atresia is generally poor, but nonlethal cases are reported.³⁵ Infants with extensive erosions often expire quickly due to fluid and electrolyte imbalances as well as sepsis. If

surgical correction of the pyloric atresia is successful, infants may still succumb to sepsis, feeding intolerance, failure to thrive, and respiratory or renal disease before 1 year of age.³⁶

Genetics and pathogenesis

JEB-H and a subset of JEB-nH gen are caused by mutations in three genes, *LAMA3*, *LAMB3*, and *LAMC2*, which encode the constitutive subunits of the basement membrane protein laminin-332.³⁷ As a component of the basal lamina, laminin-332 plays a critical role in the adhesion of keratin intermediate filaments to the basement membrane, and absent or abnormal laminin-332 leads to structural instability, manifesting as blistering through the lamina lucida. In the majority of JEB-H cases, mutations that result in premature termination codons and subsequently, absence of laminin-332 expression, are seen.^{38,39} In the case of JEB-nH, less deleterious mutations result in an abnormal laminin-332 protein that retains some degree of function.³⁹ Mutations in *COL17A1* which encodes type XVII collagen, a component of the hemidesmosome, also produce the JEB-nH gen phenotype, as well as JEB-non-Herlitz, localized.^{40,41} Mutations in three genes, *ITGB4* (~80%), *ITGA6* (~5%), and *PLEC1* (~15%) produce the EB with pyloric atresia phenotype.⁴²

DYSTROPHIC EPIDERMOLYSIS BULLOSA

DDEB may be more common than reported, as individuals with mild phenotypes may not seek medical attention. The NEBR estimated the prevalence of DDEB to be approximately 1/million,³ while Scottish data suggests a point prevalence of 1/14.6 per million.¹³ Infants with DDEB may present with CLAS and/or with blistering in the newborn period. As the child ages, the tendency for blistering decreases. Blistering most commonly affects areas predisposed to trauma, such as the hands, feet, elbows, and knees, and heals with atrophy and milia. Oral erosions occur but are often mild. Nail dystrophy is common and may be the only clinical sign of disease.⁴³ Extracutaneous complications such as esophageal strictures are uncommon. Transient bullous dermolysis of the newborn is a distinctive variant of DEB that is benign and self-limited. Blistering begins at birth or in the newborn period and dramatically improves or even remits completely, usually within the first year of life. Most reported cases are sporadic, but familial cases are described.^{44,45}

The incidence of RDEB is approximately 1–2/million live births.^{3,13} The current classification includes RDEB, severe generalized (RDEB-sev gen, formerly Hallopeau–Siemens), RDEB, generalized other (RDEB-O, formerly non-Hallopeau–Siemens), and several rare subtypes with more limited involvement (Table 11.1).

In RDEB, blistering and erosions begin at birth and can be extensive. The compromised skin barrier is a risk for infection, and during the neonatal period sepsis is the most worrisome complication. Although death can occur, infants with RDEB generally do fairly well, especially compared with infants with JEB. Affected areas heal with scarring that can lead to the development of joint contractures over time. Recurrent scarring of the hands and feet leads to loss of the interdigital spaces and eventual contracture of the digits, called pseudosyndactyly or ‘mitten’ deformities (Fig. 11.10).⁴⁶ Joint contractures and pseudosyndactyly may begin in the first year of life. Nail involvement is common with anonychia due to nail shedding and scarring of the nail bed at an early age.



Figure 11.10 The foot of a young child with RDEB. Note the erosions, chronic erythematous scarring, loss of nails, and webbing of the toes.

Extracutaneous involvement is common in RDEB, and generalized RDEB (and JEB) are effectively multisystem disorders. Mucosal involvement includes the gastrointestinal tract, ocular, and genitourinary system. Oral ulcers are painful and make eating difficult, limiting the ability of the child to take in adequate calories. Oral scarring leads to microstomia, ankyloglossia, and loss of the vestibule.⁴⁷ Esophageal involvement is extremely common; erosions lead to progressive strictures that produce dysphagia and limit adequate caloric intake. Malabsorption is another gastrointestinal complication that is poorly understood.¹⁹ Anal erosions make defecation painful, exacerbating constipation. The cornea and conjunctiva are frequent sites of ocular injury. Recurrent abrasions and ulcers lead to scarring that can affect visual acuity.⁷ Urinary tract involvement may present with dysuria, hematuria, meatal stenosis, or even sepsis. Ureterovesical obstruction and hydronephrosis can occur.⁴⁸

Failure to thrive is a common complication of generalized RDEB and results from unmet nutritional needs. Affected neonates and infants demonstrate failure to gain weight adequately before height velocity drops off. Chronic wound healing, blood and protein losses from erosions, and infection increase the body's need for calories. Oral, esophageal and intestinal involvement hinders adequate intake and absorption of nutrients. In addition to causing growth failure, chronic malnutrition contributes to poor wound healing, the development of anemia, deficiencies of essential minerals and trace elements, and increased susceptibility to infection.^{49,50} Anemia likely results from both iron deficiency and poor iron utilization due to chronic inflammation.⁵¹ Additional long-term complications of RDEB that are most often seen in older children, adolescents or adults include renal failure, osteopenia and osteoporosis, cardiomyopathy, and aggressive squamous cell carcinomas.^{7,46}

Genetics and pathogenesis

All forms of DEB are caused by mutations in the gene *COL7A1*, which encodes type VII collagen, the major component of anchoring fibrils.⁵² Each collagen VII molecule is made of three polypeptide chains that associate and assemble into a triple helix. Two collagen VII molecules align in an antiparallel fashion, and groups of these dimers form the anchoring fibrils that connect the lamina densa to anchoring plaques in

the dermis. As with other forms of EB, genotype–phenotype correlations have emerged. In the case of RDEB-sev gen, homozygous or compound heterozygous mutations resulting in premature termination codons and a subsequent lack of collagen VII are most commonly found.⁵² Less deleterious mutations, such as missense mutations or the combination of a missense mutation and a premature termination codon, are found in other forms of RDEB. Finally, DDEB is typically caused by heterozygous mutations resulting in glycine substitutions in the triple helical region of *COL7A1*.⁵² These mutations allow a full-length protein to be formed, but the substitution leads to conformational instability of the mature collagen VII protein (the so-called ‘dominant negative’ effect).

KINDLER SYNDROME

Kindler syndrome (KS) is a rare, autosomal recessive disorder in which trauma-induced blistering begins at birth or early in infancy. Based on clinical and laboratory features, it is often diagnosed as a form of EB in the neonate. However, patients with KS develop progressive poikiloderma and cutaneous atrophy in childhood.⁵³ Photosensitivity is variable. Gingivitis and periodontitis are common mucosal findings. In addition, esophageal and urogenital stenosis can occur. KS is caused by mutations in *FERMT1* which encodes fermitin family homolog 1 (kindlin-1), involved in cell–matrix interactions.⁵⁴

Differential diagnosis

When faced with a newborn with blisters and erosions, the most critical immediate task is to exclude infection, especially intra-uterine herpes simplex infection. Other potential infectious etiologies include bacterial and fungal infections and neonatal varicella. Other genetic disorders can present with bullous or erosive lesions, although these are not the predominant disease features over time. Incontinentia pigmenti presents with vesicles, and neonates with epidermolytic ichthyosis and ankyloblepharon-ectodermal dysplasia-clefting syndrome⁵⁵ can present with widespread erosions. Infants born to mothers with immune-mediated blistering disorders may also manifest transient blisters and erosions as neonates. In addition, infants may develop immune-mediated blistering disorders *de novo* (see below). Diffuse cutaneous mastocytosis may also produce extensive blistering and erosion in newborns and infants.

Evaluating suspected EB

Because an accurate diagnosis of the type and subtype of EB based on clinical findings alone is often impossible in the neonatal period, laboratory evaluation is crucial. Biopsy of an affected area for routine light microscopy is helpful in differentiating EB from other diagnoses. Additional biopsies for immunofluorescence microscopy (IFM) and, in some cases, transmission electron microscopy (TEM) are needed to rapidly and accurately diagnose the EB type and subtype. This information improves the care provider's ability to counsel and educate parents on the baby's prognosis and to guide future therapy.

While TEM was formerly considered the ‘gold standard’ for EB diagnosis, IFM testing is preferred now due to broader availability, rapid turnaround time, and lower cost.⁵⁶ The initial and most common application of IFM involves a limited panel of antibodies to BMZ proteins to map the level of the blister,

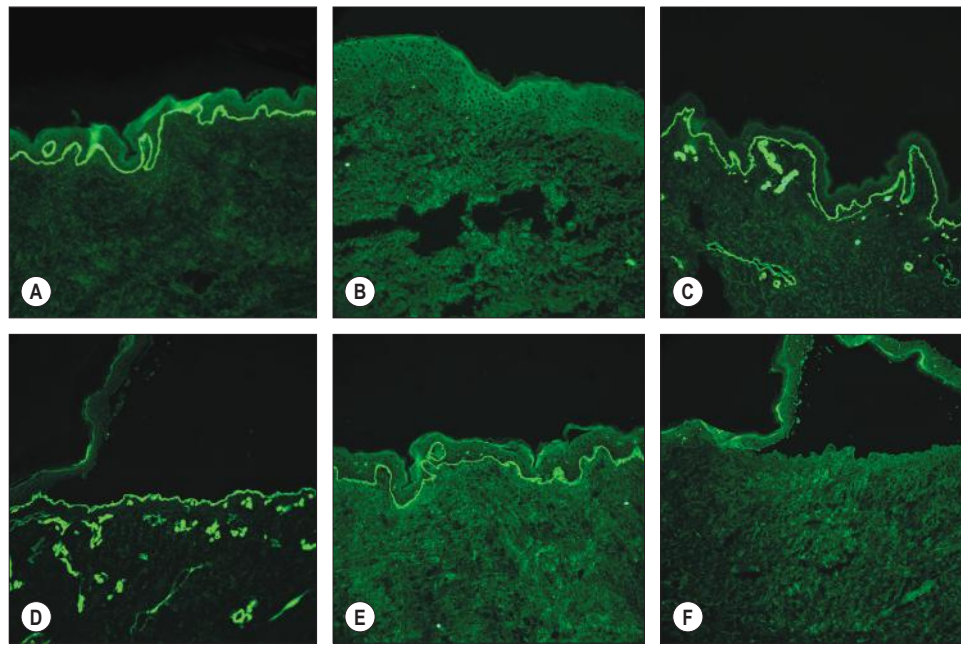


Figure 11.11 Immunofluorescence microscopy for EB. Linear staining with collagen VII antibody in normal skin (A, $\times 20$) is absent in RDEB (B, $\times 20$). Linear staining with collagen IV antibody in intact normal skin (C, $\times 20$) is present in normal intensity on the floor of an induced blister in a patient with JEB (D, $\times 20$). Linear staining with K140 (laminin-332 beta 3 chain antibody) in normal skin (E, $\times 20$) is absent in JEB, Herlitz (F, $\times 20$). (Reprinted with permission from Berk DR, Jazayeri L, Marinkovich MP, Sundram UN, Bruckner AL. Diagnosing epidermolysis bullosa type and subtype in infancy using immunofluorescence microscopy: the Stanford experience. *Pediatr Dermatol* 2013; 30(2):226–233.)

TABLE
11.2

Laboratory evaluation for epidermolysis bullosa – characteristic IFM and TEM findings

EB subtype	IFM	TEM
Lethal acantholytic EB	Absent desmoplakin (C-terminal directed antibodies must be used, limited availability)	Perinuclear retraction of KF
Plakophilin deficiency	Absent plakophilin-1 (limited availability)	Perinuclear retraction of KF, small suprabasal desmosomes
EBS, localized and other generalized	Normal	Basal cytolysis
EBS, Dowling–Meara	Normal	Basal cytolysis, clumped KF
EBS with muscular dystrophy	Reduced to absent plectin	Basal cytolysis, KF not attached to HD
EBS with pyloric atresia	Reduced to absent plectin or $\alpha 6 \beta 4$ integrin	Cleavage in basal layer, KF not attached to HD
EBS, autosomal recessive	Absent keratin 14	Few to absent KF in basal layer
JEB, Herlitz	Absent laminin-332	Cleavage in lamina lucida, reduced to absent HD
JEB, non-Herlitz	Reduced laminin-332 or reduced to absent collagen XVII	Cleavage in lamina lucida, rudimentary HD
JEB with pyloric atresia	Absent $\alpha 6 \beta 4$ integrin	Cleavage in lamina lucida, small HD
Bullous dermolysis of the newborn	Intraepidermal, granular collagen VII	Sub-lamina densa cleavage, stellate bodies in basal keratinocytes, reduced AF
DDEB, generalized	Normal	Sub-lamina densa cleavage, normal to decreased AF
RDEB, severe generalized	Absent collagen VII	Sub-lamina densa cleavage, absent AF
RDEB, generalized other	Normal to reduced collagen VII	Sub-lamina densa cleavage, reduced or rudimentary AF
Kindler syndrome	Normal, reduced or absent Kindlin-1; reduplication of lamina densa can be demonstrated using anti-type IV and anti-type VII collagen antibodies	Variable cleavage planes, fragmentation and reduplication of lamina densa

IFM, immunofluorescence microscopy; TEM, transmission electron microscopy; AF, anchoring fibril; HD, hemidesmosome; KF, keratin filament.

rapidly diagnosing the EB type. A more specific use of IFM is an expanded panel of monoclonal antibodies to proteins affected in EB, permitting the precise determination of the underlying molecular defect, based on the staining intensity (normal, reduced, or absent) of the targeted proteins (see Fig.

11.11 and Table 11.2). Unfortunately, many dermatopathology services do not maintain the antibodies needed for EB-specific IFM studies, and referral to a laboratory experienced in EB diagnosis may be required. The Stanford Dermatopathology Service (<http://dermatopathology.stanford.edu>) or Beutner

BOX 11.1 INDUCING A BLISTER FOR EB DIAGNOSIS

1. Choose an area of unaffected skin, preferably where it is easy to stabilize the baby. The upper arm, upper leg, or flank work well.
2. Mark the area that will be biopsied by drawing a small (6 mm) circle on the skin.
3. Anesthetize the area with 1% lidocaine plus epinephrine (adrenaline).
4. Using firm pressure, twist a clean pencil eraser firmly back and forth within the marked area for at least 10–15 s. If a pencil is not available, rub the marked area firmly with a gloved finger for at least 15 s. Erythema should be visible, but a blister probably will not be apparent to the naked eye.
5. Clean the skin, but do not remove the marked outline.
6. Biopsy the area, aiming for approximately one-third of the induced blister (the skin within the marked area) and two-thirds normal skin with each biopsy.

Laboratories (<http://www.beutnerlabs.com>) are two US laboratories that are recommended.

TEM is a complementary test to IFM and has advantages in certain situations. Particularly, its ability to directly visualize ultrastructural morphology is useful for diagnosing EBS-DM (keratin clumps) or in supporting the diagnosis of other forms of EB where the IFM findings are inconclusive. For example, in the case of DDEB, the diagnosis may be better supported by showing wispy or reduced anchoring fibrils on TEM than by slightly reduced collagen VII staining on IFM.

Yiasemides and colleagues⁵⁷ demonstrated the superiority of IFM over TEM in a prospective study of 30 cases of EB, in which IFM using an expanded panel of 13 monoclonal antibodies was compared to TEM, with genetic testing as the gold standard. IFM was 100% sensitive and specific for the diagnosis of either EBS or DEB, compared with 75–80% for TEM, and for the diagnosis of JEB, IFM demonstrated 90% sensitivity and 100% specificity vs 60% and 92% for TEM.

It is imperative that a freshly induced blister is biopsied, and the steps involved in inducing a blister are outlined in Box 11.1. Existing blisters, even if intact, may show signs of re-epithelialization that interferes with proper interpretation. The decision whether to use a punch or shave technique for biopsy depends on the pathologist's preference, and consultation before the biopsy is taken. At least two biopsies (one each for IFM and TEM studies) should be taken, and each should include a portion of the induced blister and a portion of normal skin. Specimens sent for IFM are placed in Zeus or Michel's fixative, and TEM specimens should be stored in glutaraldehyde.

DNA mutation analysis can be used to confirm the clinical and pathologic diagnosis. It is most accurate when testing can be directed toward a particular gene. Therefore, it is recommended that the EB subtype be diagnosed by IFM and/or TEM analysis before genetic testing is ordered. Genetic testing may be helpful in cases where the clinical and pathologic findings are indistinguishable, such as distinguishing mild RDEB from DDEB. Knowing a child's mutation also helps guide genetic counseling and facilitates prenatal diagnosis in future pregnancies. Testing all of the known genetic causes of EB simultaneously is now possible. However, gene testing is time-consuming, and results will probably not be available until several weeks after the test is ordered. Thus, it is not reasonable at this time to rely solely on genetic testing for diagnostic or prognostic

counseling in the neonatal period. DNA analysis for EB is available in the USA through the commercial company GeneDx (www.genedx.com).

Prenatal diagnosis of EB was formerly available only by fetal skin biopsy, but is now more commonly performed using DNA mutation analysis from cells obtained via chorionic villus sampling or amniocentesis.⁵⁸ In these cases, known mutations in affected siblings and/or parents are needed to guide testing and decision-making regarding the fetus. Preimplantation genetic diagnosis for potentially lethal EB phenotypes is also possible.⁵⁸

Management of EB in neonates and infants

The prospect of caring for a child with EB often induces anxiety in both parents and care providers. Many activities integral to the newborn period, such as diapering, feeding, or simply picking up the infant, can induce more blisters and compound this unease. While EB is not currently curable, treatment is aimed at maintaining the health of the child and supporting the psychosocial well-being of the family. Immediate goals in the newborn period are to: (1) promote wound healing; (2) prevent and treat infection; (3) minimize pain and discomfort; (4) provide optimal nutrition and support adequate growth, and (5) facilitate normal bonding between the infant and family.

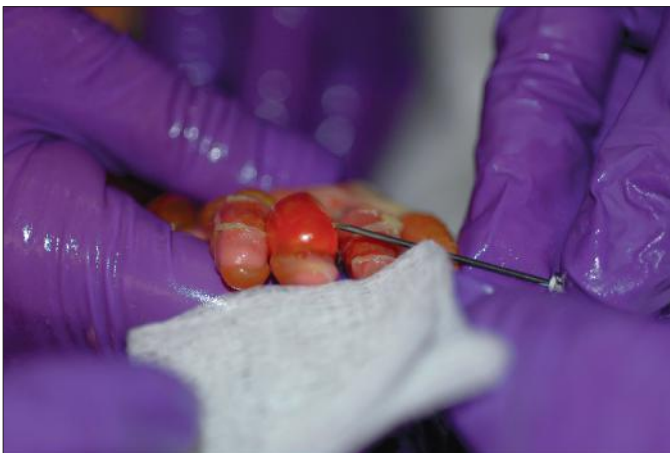
Newborns with presumed EB are best cared for in a nursery or neonatal intensive care unit with experience in treating EB. A neonatologist or pediatrician may oversee the care, with the dermatologist providing guidance on the diagnostic work-up, wound care, and other disease-specific aspects of treatment. Other specialists may also be needed, depending on the baby's particular complications. A skilled nurse, particularly one with experience in wound care, is another critical component of the EB care team.

The goals of EB management in the newborn period are outlined in Table 11.3. In addition, attention should be paid to basic needs such as fluid and electrolyte balance and temperature control. Skin erosions may result in increased fluid loss and electrolyte alterations, such as hypernatremia. If the infant is not feeding well, intravenous fluids may be needed, and electrolytes should be checked as needed until stable. Monitoring the baby will likely be easier from an open bed instead of an enclosed isolette. Temperature control can be aided by the use of a radiant warmer with heat output at a minimal setting. The environment should not be too warm, however, as this may promote blistering.^{59,60} Temperature probes or other monitoring devices should not be taped to the skin.

Given the nature of EB, it is impossible to completely prevent new blisters from forming, but by minimizing trauma to the skin and mucosa, it is possible to limit their frequency and severity. As even minimal trauma can produce blisters, careful handling of the baby is paramount.^{59,60} Tape or adhesives should not be used on the skin as their removal produces blistering. If medical devices need to be secured, they may be fastened to dressings or a self-adhesive compression wrap (e.g., Coban™, 3M) can be used. Mepitac® (Mölnlycke Health Care), a silicone 'tape' that does not contain adhesives, can be used on fragile skin, but should be used with care in those EB subtypes with excessive skin fragility. Friction often occurs where clothes or diapers rub the skin. Cloth diapers may be less traumatic around the waistband and thigh areas. Alternatively, the elastic cuffs can

TABLE 11.3 Objectives of EB management in the neonatal period

Objective	Plan
Accurately diagnose the EB type and subtype	Use clinical history, cultures, histology to rule out etiologies other than EB Biopsy an induced blister for immunofluorescence microscopy and transmission electron microscopy studies
Minimize new blisters and erosions	Consider genetics consultation and genetic testing Mandate gentle handling and reduce friction on the skin Forbid tape or adhesives on the skin
Promote wound healing	Inspect the skin and bandages daily Plan for daily to every other day cleansing of the skin and bandage changes, depending on the degree of exudate from the wounds
Prevent infection	Thoroughly wash hands or use alcohol-based hand sanitizers before and after patient care Place the baby in protective contact isolation (i.e., use gowns and gloves when handling the baby) Culture areas suspicious for infection and treat infection accordingly
Promote comfort and control pain	Use oral sucrose with dressing changes Consider acetaminophen or short-acting narcotics Use sucralfate for oral ulcers Treat gastroesophageal reflux
Optimize nutrition	Follow weight daily Fortify breast-milk or formula Use soft nipples or cleft lip and palate feeder Begin a daily multivitamin
Support the family	Promote normal bonding between the baby and family Referral to Dystrophic Epidermolysis Bullosa Research Association (DEBRA)

**Figure 11.12** Bullae being punctured with a sterile needle to prevent lesion extension.

be cut out of disposable diapers, minimizing blistering on the thighs. Seams from clothing may also produce blisters. Clothing should be soft and loose fitting, and if flat seams are not available the clothing should be turned inside out. The baby should not be lifted under the arms; instead, the head and buttocks should be supported at all times. To minimize blistering on the back, soft padding such as a sheepskin should be used to line the bed (which should remain flat), and a disposable underpad covered with a thin layer of petroleum jelly or a similar ointment will help minimize friction.

For existing blisters and erosions, wound care is essential to promote healing and prevent infection. Bandaging also provides protection to the skin and helps limit future blistering.^{61,62} Wound care should be performed daily to every other day, depending on the nature of the wounds. The complete task of bathing and redressing the baby can take up to 2 h to complete and needs two people working together to run smoothly. Having

all the necessary materials prepared ahead of time greatly speeds up the task (Table 11.4).

To minimize trauma to exposed skin, it is best to clean and bandage the baby one part at a time. For instance, wound care can be performed on each extremity, followed by the torso and then the face and scalp. Bandages should be removed gently. If they are adherent to the wound, they should be soaked off with saline or dabbed with a petrolatum-based ointment until soft. Bandages should never be forcibly removed – this is both painful and disrupts the healing process.⁶² The skin should then be cleaned with a saline or mild soap or cleanser and water, and gently patted dry with a soft towel. The skin should not be rubbed. Existing erosions should be assessed for signs of infection and for evidence of healing. In order to prevent extension of existing lesions, intact blisters should be drained by puncturing the dependent side using a sterile needle or lancet (Fig. 11.12) and using sterile gauze to wick away blister fluid.^{59–61} The blister roof should be left in place unless it hangs freely. Redundant skin or crust can be gently trimmed away with clean, sharp scissors, but aggressive debridement is not indicated.

The skin should then be covered with dressings. Ideal dressings for EB patients should be nonadherent and promote a moist, healthy wound bed.^{61,63,64} Many products fulfill these criteria, and the ultimate decision on which ones are used depends on their availability, cost, and the physician (and later parent) preference. The contact layer, the first bandage to cover the wound, should be nonadherent. Silicone dressings are generally preferred as they release easily from the wound and intact skin without causing additional trauma. Mepitel® (Mölnlycke Health Care) is a fenestrated silicone contact layer that clings gently to noninjured skin and is easily removed by moistening it with water. Another common nonadherent dressing is petrolatum-impregnated gauze. If such a product is used, it should be ‘buttered’ with a liberal amount of an emollient such as petroleum jelly or Aquaphor® healing ointment (Beiersdorf Inc.) first. This prevents the wound from drying out and reduces the likelihood of the bandage sticking to the wound.

TABLE 11.4 Typical items needed for epidermolysis bullosa dressing changes

Item	Purpose
Warm saline or water and mild cleanser	To clean the skin and wounds
Sterile needles and sterile gauze	To lance and drain intact blisters
Sterile sharp scissors	To trim excess or hanging skin
Preservative-free, petrolatum-based ointment	To emolliate the skin and provide moisture to the wounds; to prevent bandages from adhering to wounds
Petrolatum-impregnated gauze, Mepitel [®] , or similar contact layer	Contact layer, applied directly over wounds
Foam or absorbent dressing	Absorbent layer, soaks up exudate and protects noninjured skin
Retention dressing (rolled gauze, elastic tubular dressing)	Holds dressings in place



Figure 11.13 Infant with RDEB having digits wrapped with petrolatum-impregnated gauze.



Figure 11.14 Evidence of healing and re-epithelialization in extensive ulcers after 2 weeks of wound care.

Absorptive dressings are then applied over the contact layer. These soak up exudate and provide padding and protection for the child. Foam dressings such as Mepilex®, Mepilex Lite®, and Mepilex Transfer® (Mölnlycke Health Care) and Allevyn® (Smith & Nephew) combine a contact layer with absorptive material and can be used directly on the skin. Dressings should then be secured with layers of conformable rolled gauze and stretchable burn netting or a tubular retention dressing. For infants with RDEB and digital erosions, separating the digits with strips of petrolatum-impregnated gauze and wrapping the fingers individually may help delay the onset of webbing and pseudosyndactyly (Fig. 11.13). With good wound care, even extensive erosions will show excellent healing within 1–2 weeks (Fig. 11.14).

The prophylactic use of topical antibiotics is not recommended for wounds that appear clean. Signs of wound infection include increased erythema, drainage, odor, crusting, or tenderness. Although wound infection is a clinical diagnosis, wound cultures can be used to guide antibiotic therapy. Minor wound infections often improve with the use of topical antibiotics and dressings that help to wick away excess exudate. Common topical antibiotics include bacitracin, mupirocin, and gentamicin ointments. It is best to limit the duration of use of topical antibiotics to periods of suspected infection. They should be discontinued when the wound appears clean, or rotated every 1–2 months to prevent resistance.^{63,65} Bathing with dilute bleach

or vinegar in the bath may also be useful to reduce the bacterial load on the skin and may help minimize reliance on topical antibiotics. Two teaspoons of undiluted bleach per gallon of water is one recommended concentration. Systemic antibiotics are indicated for extensive and/or invasive infection. Open erosions act as portals of entry for bacteria, and sepsis is a complication of EB in the neonatal period. Neonates with presumed cellulitis or sepsis should be treated with broad-spectrum systemic antibiotics, which should be subsequently narrowed based on wound and blood culture results.

In addition to the calories needed for normal growth, neonates and infants with extensive erosions have added metabolic demands due to wound healing. Failing to account for this contributes to failure to thrive in children with JEB and RDEB. However, obtaining adequate nutrition in EB can be a management challenge, especially when oral erosions and ulcers make feeding painful and laborious. Mothers who choose to breast-feed should be supported, but suckling can aggravate oral erosions, and breast milk alone may not meet the nutritional needs of an infant with EB. For those infants at high risk for failure to thrive, it may be preferable to express and then fortify the breast-milk. Likewise, high-calorie formulas should be started for infants with JEB and RDEB that are formula fed, even before signs of poor weight gain are seen.⁴⁹ The simple act of using growth charts to follow weight and height cannot be forgotten. Declines in the velocity of weight gain signify the patient is not getting adequate calories and need to be addressed promptly. The early input of the gastroenterology and nutrition team can be very helpful. Nipples should be soft and preferably high flow, so that the infant does not need to suck vigorously. A cleft lip and palate nurser, such as the Haberman® feeder (Medela) may also be helpful. In rare instances, a soft nasogastric (NG) tube may be used as a temporary intervention to aid in feeding. However, NG tubes should be placed with caution as they may cause trauma to the oral mucosa and esophagus and promote the development of strictures.

Introduction of soft solid foods should begin at 4–6 months of age and advanced slowly as tolerated. Patients with severe EB may not tolerate solid foods well due to trauma and scarring of the oral mucosa, and the development of feeding coordination can be delayed. The input of an experienced feeding therapist can be invaluable. Many patients remain dependent on calorically-dense liquid supplements to meet their caloric needs throughout their life. Infants with feeding difficulties or failure to thrive may benefit from the placement of a gastrostomy tube to deliver nutrition and medications. Gastrostomy tubes can be used to meet some, most, or all of a patient's nutritional needs, depending on the ability to take foods by mouth. Daily requirements for vitamins and minerals are likely increased in patients with EB, possibly due to increased utilization for metabolism and wound healing, along with inadequate intake and absorption. It is not uncommon to find patients with low levels of iron, zinc, and vitamin D.⁶⁶ All infants with EB should be started on a daily multivitamin, ideally with iron.

The blisters and erosions of EB, both on the skin and internally, are painful, and most patients report living with chronic pain.^{67,68} In addition, pain is often exacerbated by procedures such as dressing changes and bathing. Pain management in EB is a challenge, owing to the chronic nature of the disease. Proper wound care is a 'topical' form of pain control.⁶¹ The discomfort of bathing may be alleviated by adding pool salts to the water to approximate normal saline and allow the water to be isotonic

with open wounds.⁶⁹ In infants with extensive erosions, systemic pain medications may be needed, especially with dressing changes. Medications should be given 20–30 min before beginning bandaging. Acetaminophen may be tried first, and if this is not sufficient, an opiate agonist can be added.⁶⁸ Oral sucrose is effective to control procedural pain in neonates and may also be used,⁷⁰ although it has not been specifically evaluated for EB. Oral discomfort may be controlled with topical analgesics before feeding. The use of sucralfate to coat ulcers is also effective.⁷¹ The use of eye ointments to prevent and treat corneal erosions reduces eye pain. Gastroesophageal reflux may also be painful, especially if the child has esophageal erosions. The use of an H2 blocker or proton-pump inhibitor in these cases reduces pain.¹⁹

It should not be forgotten that a baby with EB is a baby, and normal bonding with the parents should be encouraged and a caregiver's voice and touch is important to the child. However, having a newborn with EB is a life-altering experience, and the parents may need time to adjust. The medical team must be able to provide psychosocial support for the family. An excellent resource for families affected by EB is the Dystrophic Epidermolysis Bullosa Research Association (DEBRA, www.debra.org, www.debra-international.org). In addition to providing excellent information geared toward a lay audience, DEBRA offers consultation with an EB nurse specialist.

ADDITIONAL CONSIDERATIONS

In those cases where neonates present with extracutaneous manifestations requiring surgical intervention, such as pyloric stenosis or respiratory distress in the case of suspected JEB-H, the risks and benefits of surgical intervention must be weighed against the child's overall prognosis. With careful attention, patients with EB can tolerate intubation (either nasopharyngeal or endotracheal) and anesthesia for procedures.^{72,73} Repair of pyloric atresia³⁶ and early placement of tracheostomy tubes²⁹ have been performed successfully in EB patients, but these infants often succumb to other complications of their disease. Thus, comfort care alone is a valid treatment option for infants with EB subtypes that carry a poor prognosis, such as JEB-PA and JEB-H.^{31,74}

In order to be discharged after birth, infants with EB need to be medically stable. From a dermatologic standpoint, a reasonable goal is no more than 10% skin involvement, minimal development of new blisters, and evidence of adequate feeding and weight gain. In addition, parents or care providers should demonstrate comfort with and competence at changing the baby's dressings, and support services such as a home health nurse and sufficient medical supplies need to be in place. Infants should have follow-up with care providers who are experienced in managing EB. A multidisciplinary approach is needed to monitor for and treat the many complications that may develop as the child ages.

Protocols for optimal follow-up after discharge are not standardized, but clinic visits at least every 3 months in the first year of life are a good rule of thumb, with more frequent follow-up being needed for infants with severe disease. In addition to monitoring skin involvement, growth and development should be followed closely with the pediatrician. Many infants with EB will lag in motor development, and having a physical therapist and occupational therapist involved in the treatment plan to address gross and fine motor development is important. Due to

a high risk for dental complications, visits with a pediatric dentist should also begin in the first year of life.⁷⁵ Any infant with EB and signs and symptoms of anemia, such as fatigue, pallor, and tachycardia, should have blood work performed. However, as anemia is common in severe forms of EB and as the signs and symptoms may be difficult to appreciate, all infants with JEB and RDEB should have a screening complete blood count and iron studies performed by 1 year of age, and repeated every 6–12 months thereafter.

Finally, families of infants with EB should be encouraged to maintain hope as disease-specific treatments that show promise are becoming available. A landmark study demonstrated that keratinocyte stem cells from an adult patient with JEB-nH were genetically corrected and successfully transplanted back to affected areas of the legs, resulting in normal, robust skin during the 1-year follow-up period.⁷⁶ This technique is being investigated as a treatment for RDEB.⁷⁷ Bone marrow transplant has been shown to increase expression of collagen VII at the basement membrane zone and reduces the severity of disease, although there is significant risk with this approach.⁷⁸ Replacement of collagen VII,^{79,80} either locally or systemically, is another therapy that is hoped will be available for RDEB on an experimental basis soon.

Acquired blistering diseases

AUTOIMMUNE BULLOUS DISORDERS

Autoimmune bullous disorders (AIBD) are a heterogeneous group of acquired blistering skin diseases due to pathogenic circulating antibodies targeted against structural adhesion molecules of the skin and mucous membranes. Transient bullous disorders (see [Chapter 10](#)) can occur in neonates born to mothers with active or quiescent AIBD, such as pemphigus vulgaris,^{81–83} pemphigus foliaceus,^{84,85} epidermolysis bullosa acquisita,⁸⁶ and pemphigoid gestationis.^{87,88} In these cases, maternal IgG antibodies cross the placenta and cause symptoms in the neonate. The estimated plasma elimination half-life of IgG is 15 days, and disease resolution typically parallels clearance of the antibodies. Supportive therapy is usually sufficient for this duration, although topical corticosteroids may be beneficial for patients with a significant inflammatory presentation.⁸⁹

AIBD also arise in neonates and children due to the *de novo* generation of autoantibodies. These disorders are quite rare, and presentation in the first 2 years is uncommon. There is significant morphologic overlap between the variants, making clinical diagnosis imperfect. Histopathology and immunofluorescence (IF) are required to identify the target antigen(s) and establish a definitive diagnosis. In addition to the disorders discussed below, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, and dermatitis herpetiformis are AIBD to consider in the differential diagnosis of bullous and erosive lesions,⁹⁰ but their presentation in infants is unlikely.

Linear IgA disease

Linear IgA disease (LAD, also known as linear IgA bullous dermatosis, chronic bullous disease of childhood) is the most common AIBD of childhood, typically occurring between 6 months and 5 years of age. Disease onset in the neonatal period has been reported, albeit infrequently, and case reports suggest that neonatal onset can be associated with significant morbidity



Figure 11.15 Linear IgA disease. Annular blisters on an erythematous base.



Figure 11.17 Bullae on the feet of an infant with bullous pemphigoid. (Courtesy of Dr Brid O'Donnell.)



Figure 11.16 Widespread bullous pemphigoid in an infant. Note how some of the lesions have an annular appearance, similar to linear IgA disease.

due to mucosal involvement.^{91–93} As the name suggests, the diagnosis relies on immunopathological findings: the exclusive or predominant presence of linear deposits of IgA along the BMZ.⁹⁴ Disease onset is typically abrupt, and may be associated with pyrexia, malaise or other prodromal symptoms.⁹⁵ The mean disease duration is 3–5 years, after which the majority of patients achieve complete remission, and disease rarely persists or recurs in adulthood.^{96,97}

Clinically, LAD is characterized by the presence of clear or hemorrhagic vesicles, bullae or erosions that vary in size, arising from normal skin or urticarial plaques (Fig. 11.15). New lesions tend to occur at the periphery of older ones forming rosettes or clusters.⁹⁸ Bullae are usually tense, and may mimic lesions of bullous pemphigoid (Fig. 11.16). Lesions are predominantly localized to the lower abdomen, neck and perineal areas, with prominent anogenital involvement. Mucosal involvement is more common in the pediatric setting, affecting up to 76% of children, and may be associated with significant morbidity.^{99,100}

Oral lesions usually present as erosions and ulcerations, and predominantly affect the hard and soft palate, buccal mucosa and gingiva, with relative sparing of the lips. Ocular involvement is also common in the pediatric setting and occurs in up to 65% of patients, with scarring occurring in 43% of patients who report symptoms.¹⁰¹ It may appear as isolated conjunctival injection and can result in scarring with subconjunctival fibrosis and symblepharon formation.^{101,102} Other mucosal membranes may be involved, and are also at risk of scarring, including the larynx, pharynx, trachea, esophagus, bronchial tree, and vaginal mucosae.

Fresh blisters on routine histopathology may be suggestive, but not diagnostic, showing subepidermal blistering with an inflammatory infiltrate consisting of neutrophils and eosinophils. Skin biopsy of perilesional unaffected skin for direct IF is mandatory to establish the diagnosis. IF shows a linear deposit of IgA antibodies at the BMZ. C3, IgG or IgM may be seen as well, but the predominance of IgA is needed to establish the diagnosis.⁹⁸ The multiplicity and complexity of target antigens is likely due to epitope spreading. Circulating IgA antibodies, although usually present in low titers, are detectable in 80% of children, a higher proportion than occurs in adults.^{100,103}

Therapeutic options include potent topical steroids for mild cases or mucosal lesions which are often resistant to systemic therapies. Systemic therapy is required until patients enter complete clinical remission, followed by maintenance therapy until the disease remits. Prednisolone (0.5–2 mg/kg per day) is often used first to attain disease control, but should be combined with other therapies and tapered in order to minimize adverse effects. Dapsone (0.5–3 mg/kg per day) is considered the treatment of choice beyond the neonatal period. Other options include erythromycin (50 mg/kg per day), IVIG (400–2000 mg/kg per cycle), and tacrolimus 0.03% topically BD. Mycophenolate mofetil (300–600 mg/m²), and cyclosporine



Figure 11.18 Urticarial, annular plaques on the arms of an infant with bullous pemphigoid. (Courtesy of Dr Brid O'Donnell.)

(2.5–5 mg/kg per day) have shown good efficacy in older children refractory to other therapies.^{104,105}

Bullous pemphigoid

Childhood bullous pemphigoid (BP) is an IgG-mediated subepidermal bullous disorder. It is rare in childhood, with peak prevalence in the 1st and 8th years of life.^{106–109} Some 50% of cases present under 12 months of age, with the earliest reported cases occurring at 2 months of age.^{108,110} Mucous membrane involvement, acral distribution, and facial involvement appear to occur more frequently in childhood BP, and lesions tend to involve the palms and soles of infants of less than 1 year (Fig. 11.17).¹⁰⁸ Lesions of BP may begin as urticarial, irregularly bordered plaques reminiscent of erythema multiforme, evolving into widespread, tense blisters on erythematous or clinically unaffected skin, frequently located on the trunk and flexural areas (Fig. 11.18).¹⁰⁹ Pruritus is often prominent. A limited vulvar variant is recognized and can be mistaken for sexual abuse.¹¹¹ The course of childhood BP is usually indolent, and once appropriate treatment is instigated, remissions typically occur within 1 year.^{112,113}

The target autoantibodies in BP are the 180 kD or 230 kD bullous pemphigoid antigens (BP180 or BP 230).¹⁰⁶ Lesional histology shows subepidermal blister formation with an intact epidermis and a predominantly eosinophilic infiltrate. Direct IF is characterized by linear deposition of IgG and C3, however IgM and IgA may be found.^{114,115} Indirect IF can show circulating autoantibodies directed against the epidermal side of 1.0M sodium chloride (NaCl) split skin.

Oral prednisolone (0.5–2 mg/kg per day) is the mainstay of therapy, but erythromycin, IVIG, and dapsone may be useful alternative or adjunctive therapies.^{108,110,116–119}

Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita (EBA) is a rare AIBD characterized by autoantibodies to type VII collagen, the major component of anchoring fibrils. EBA has been reported as early as 3 months of age. It is exceptionally rare; less than 50 cases have been reported in the pediatric literature.^{120,121} Two phenotypes of EBA are recognized: the classic presentation with a noninflammatory mechanobullous phenotype, resembling the

dystrophic form of inherited EB; and less frequently an inflammatory presentation that mimics other AIBD. Children less than 5 years of age are more likely to present with the inflammatory type, and mucosal involvement is also thought to occur more frequently.¹²¹ Ocular involvement, which may be associated with visual loss, has been reported to occur more commonly in IgA-mediated EBA. The IgA variant, however, accounts for a minority of childhood EBA; the majority are mediated by IgG autoantibodies.^{102,122–124} In contrast to adult EBA, which is often refractory to therapy, children with EBA typically respond well to therapies such as low-dose corticosteroids and dapsone.¹²⁵ Other therapeutic options include colchicine, dapsone, infliximab, and IVIG.^{126,127}

Bullous systemic lupus erythematosus

The bullous variant of systemic lupus erythematosus (SLE) is rarely seen in children, although an isolated case of neonatal lupus erythematosus presenting with overt blistering has been reported.¹²⁸ Autoantibodies to type VII collagen have been reported as pathogenic in bullous SLE, however autoantibodies to a variety of other molecules involved in dermal–epidermal adhesion have been found, including BP antigen 1, laminin-332, and laminin-331.^{129,130} Bullous SLE may be difficult to differentiate from EBA, as the direct IF pattern is similar; patients should fulfill diagnostic criteria for SLE to establish the diagnosis.¹³¹

NON-AUTOIMMUNE BULLOUS DISORDERS

A range of other disorders may present with blisters and erosions in addition to other changes and must be considered in the differential diagnosis. Toxin-producing strains of *Staphylococcus aureus* (see Chapter 12) can produce localized flaccid bullae that quickly progress to erosions (bullous impetigo) or the generalized eruption of staphylococcal scalded skin syndrome. Viral infections with herpes simplex virus and varicella zoster virus (see Chapter 13) produce grouped or isolated vesicles on a base of erythematous skin. In any ill-appearing child with the abrupt onset of blisters, toxic epidermal necrosis (TEN) and Stevens–Johnson syndrome (SJS) (see Chapter 20) must be excluded. Wells syndrome, a rare disorder characterized by pruritic, erythematous plaques mimicking cellulitis, can also sometimes be bullous (see Chapter 20).

Mastocytosis (see Chapter 28) is a disorder of clonal mast cell proliferation that commonly affects the skin. Three cutaneous variants are recognized: mastocytomas (discrete plaques or nodules), maculopapular (often called urticaria pigmentosa) and diffuse cutaneous mastocytosis (DCM). All cutaneous variants can manifest with cutaneous blistering,^{132–136} although DCM is most likely to be problematic. In DCM, there is widespread erythroderma and blistering which usually presents in the first year of life, with a congenital presentation in 25% of cases.¹³⁷ The clinical presentation is broadly divided into two phenotypes; patients presenting with blistering on a background of erythema and urticarial plaques, or presentation with indurated leathery skin and minimal blistering. Sudden release of mast cell mediators results in pruritus, flushing, urticaria, blistering, tachycardia, hypotension, wheeze, diarrhea, abdominal pain, melena, and shock.¹³³ Mortality in the neonatal period has been reported as high as 23% of cases, due to overwhelming mast cell degranulation, sepsis or mast cell leukemia.¹³⁸

Blistering in mastocytosis usually resolves by 1–3 years; skin lesions improved in 71% in one series by 1 year of life, and 90% are symptom-free by puberty.¹³⁹ Therapeutic strategies aim to control symptoms of mast cell degranulation and to block their proliferation. The key to management is avoidance of agents that trigger histamine release, including heat, friction, polymyxin B sulfate, narcotics and NSAIDs. Symptomatic approaches include non-sedating H1 and H2 antihistamines, topical and

systemic corticosteroids, oral sodium cromoglycate for intestinal complaints, ketotifen, PUVA, and antiseptic measures because of high risk of sepsis.

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KEY REFERENCES

1. Fine JD, Eady RA, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *J Am Acad Dermatol* 2008;58(6):931–50.
24. Bolling MC, Lemmink HH, Jansen GH, et al. Mutations in KRT5 and KRT14 cause epidermolysis bullosa simplex in 75% of the patients. *Br J Dermatol* 2011;164(3):637–44.
31. Yuen WY, Duipmans JC, Molenbuur B, et al. Long-term follow-up of patients with Herlitz-type junctional epidermolysis bullosa. *Br J Dermatol* 2012;167(2):374–82.
49. Haynes L. Nutrition for children with epidermolysis bullosa. *Dermatol Clin* 2010;28(2):289–301.
63. Lara-Corrales I, Arbuckle A, Zarinehbab S, et al. Principles of wound care in patients with epidermolysis bullosa. *Pediatr Dermatol* 2010;27(3):229–37.
64. Pope E, Lara-Corrales I, Mellerio J, et al. A consensus approach to wound care in epidermolysis bullosa. *J Am Acad Dermatol* 2012;67(5):904–17.
68. Goldschneider KR, Lucky AW. Pain management in epidermolysis bullosa. *Dermatol Clin* 2010;28(2):273–82.
89. Lara-Corrales I, Pope E. Autoimmune blistering diseases in children. *Semin Cutan Med Surg* 2010;29(2):85–91.
90. Sansaricq F, Stein SL, Petronic-Rosic V. Autoimmune bullous diseases in childhood. *Clin Dermatol* 2012;30(1):114–27.
126. Meurer M. Immunosuppressive therapy for autoimmune bullous diseases. *Clin Dermatol* 2012;30(1):78–83.

REFERENCES

1. Fine JD, Eady RA, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *J Am Acad Dermatol* 2008;58(6):931–50.
2. Groves RW, Liu L, Dopping-Hepenstal PJ, et al. A homozygous nonsense mutation within the dystonin gene coding for the coiled-coil domain of the epithelial isoform of BPAG1 underlies a new subtype of autosomal recessive epidermolysis bullosa simplex. *J Invest Dermatol* 2010;130(6):1551–7.
3. Fine JD, Johnson LB, Suchindran C, et al. The epidemiology of inherited epidermolysis bullosa. In: Fine JD, Bauer EA, McGuire J, et al, editors. *Epidermolysis bullosa: clinical, epidemiologic, and laboratory advances and the findings of the National Epidermolysis Bullosa Registry*. Baltimore: Johns Hopkins University Press; 1999. p. 101–13.
4. Bart BJ, Gorlin RJ, Anderson VE, et al. Congenital localized absence of skin and associated abnormalities resembling epidermolysis bullosa. A new syndrome. *Arch Dermatol* 1966;93(3):296–304.
5. Christiano AM, Bart BJ, Epstein EH Jr, et al. Genetic basis of Bart's syndrome: a glycine substitution mutation in type VII collagen gene. *J Invest Dermatol* 1996;106(4):778–80.
6. Chung HJ, Uitto J. Epidermolysis bullosa with pyloric atresia. *Dermatol Clin* 2010;28(1):43–54.
7. Fine JD, Mellerio JE. Extracutaneous manifestations and complications of inherited epidermolysis bullosa: part I. Epithelial associated tissues. *J Am Acad Dermatol* 2009;61(3):367–86.
8. Jonkman MF, Pasmooij AM, Pasmans SG, et al. Loss of desmoplakin tail causes lethal acantholytic epidermolysis bullosa. *Am J Hum Genet* 2005;77(4):653–60.
9. Bolling MC, Veenstra MJ, Jonkman MF, et al. Lethal acantholytic epidermolysis bullosa due to a novel homozygous deletion in DSP: expanding the phenotype and implications for desmoplakin function in skin and heart. *Br J Dermatol* 2010;162(6):1388–94.
10. Hobbs RP, Han SY, van der Zwaag PA, et al. Insights from a desmoplakin mutation identified in lethal acantholytic epidermolysis bullosa. *J Invest Dermatol* 2010;130(11):2680–3.
11. McGrath JA, McMillan JR, Shemanko CS, et al. Mutations in the plakophilin 1 gene result in ectodermal dysplasia/skin fragility syndrome. *Nat Genet* 1997;17(2):240–4.
12. McGrath JA, Mellerio JE. Ectodermal dysplasia-skin fragility syndrome. *Dermatol Clin* 2010;28(1):125–9.
13. Horn HM, Priestley GC, Eady RA, et al. The prevalence of epidermolysis bullosa in Scotland. *Br J Dermatol* 1997;136(4):560–4.
14. Horn HM, Tidman MJ. The clinical spectrum of epidermolysis bullosa simplex. *Br J Dermatol* 2000;142(3):468–72.
15. Horn HM, Tidman MJ. Quality of life in epidermolysis bullosa. *Clin Exp Dermatol* 2002;27(8):707–10.
16. Buchbinder LH, Lucky AW, Ballard E, et al. Severe infantile epidermolysis bullosa simplex. Dowling-Meara type. *Arch Dermatol* 1986;122(2):190–8.
17. McGrath JA, Ishida-Yamamoto A, Tidman MJ, et al. Epidermolysis bullosa simplex (Dowling-Meara). A clinicopathological review. *Br J Dermatol* 1992;126(5):421–30.
18. Shemanko CS, Horn HM, Keohane SG, et al. Laryngeal involvement in the Dowling-Meara variant of epidermolysis bullosa simplex with keratin mutations of severely disruptive potential. *Br J Dermatol* 2000;142(2):315–20.
19. Freeman EB, Kogelmeier J, Martinez AE, et al. Gastrointestinal complications of epidermolysis bullosa in children. *Br J Dermatol* 2008;158(6):1308–14.
20. Fischer T, Gedde-Dahl T Jr. Epidermolysis bullosa simplex and mottled pigmentation: a new dominant syndrome. I. Clinical and histological features. *Clin Genet* 1979;15(3):228–38.
21. Reznicek GA, Walko G, Wiche G. Plectin gene defects lead to various forms of epidermolysis bullosa simplex. *Dermatol Clin* 2010;28(1):33–41.
22. Chiaverini C, Charlesworth A, Meneguzzi G, et al. Epidermolysis bullosa simplex with muscular dystrophy. *Dermatol Clin* 2010;28(2):245–55, viii.
23. Forrest K, Mellerio JE, Robb S, et al. Congenital muscular dystrophy, myasthenic symptoms and epidermolysis bullosa simplex (EBS) associated with mutations in the PLEC1 gene encoding plectin. *Neuromuscul Disord* 2010;20(11):709–11.
24. Bolling MC, Lemmink HH, Jansen GH, et al. Mutations in KRT5 and KRT14 cause epidermolysis bullosa simplex in 75% of the patients. *Br J Dermatol* 2011;164(3):637–44.
25. Irvine AD. Inherited defects in keratins. *Clin Dermatol* 2005;23(1):6–14.
26. Irvine AD, Rugg EL, Lane EB, et al. Molecular confirmation of the unique phenotype of epidermolysis bullosa simplex with mottled pigmentation. *Br J Dermatol* 2001;144(1):40–5.
27. Harel A, Bergman R, Indelman M, et al. Epidermolysis bullosa simplex with mottled pigmentation resulting from a recurrent mutation in KRT14. *J Invest Dermatol* 2006;126(7):1654–7.
28. Charlesworth A, Chiaverini C, Chevrant-Breton J, et al. Epidermolysis bullosa simplex with PLEC mutations: new phenotypes and new mutations. *Br J Dermatol* 2013;168(4):808–14.
29. Fine JD, Johnson LB, Weiner M, et al. Tracheo-laryngeal complications of inherited epidermolysis bullosa: cumulative experience of the national epidermolysis bullosa registry. *Laryngoscope* 2007;117(9):1652–60.
30. Fine JD, Johnson LB, Weiner M, et al. Cause-specific risks of childhood death in inherited epidermolysis bullosa. *J Pediatr* 2008;152(2):276–80.
31. Yuen WY, Duipmans JC, Molenbuur B, et al. Long-term follow-up of patients with Herlitz-type junctional epidermolysis bullosa. *Br J Dermatol* 2012;167(2):374–82.
32. Yancey KB, Hintner H. Non-Herlitz junctional epidermolysis bullosa. *Dermatol Clin* 2010;28(1):67–77.
33. Nakano A, Pulkkinen L, Murrell D, et al. Epidermolysis bullosa with congenital pyloric atresia: novel mutations in the beta 4 integrin gene (ITGB4) and genotype/phenotype correlations. *Pediatr Res* 2001;49(5):618–26.
34. Azarian M, Dreux S, Vuillard E, et al. Prenatal diagnosis of inherited epidermolysis bullosa in a patient with no family history: a case report and literature review. *Prenat Diagn* 2006;26(1):57–9.
35. Dang N, Klingberg S, Rubin AI, et al. Differential expression of pyloric atresia in junctional epidermolysis bullosa with ITGB4 mutations suggests that pyloric atresia is due to factors other than the mutations and not predictive of a poor outcome: three novel mutations and a review of the literature. *Acta Derm Venereol* 2008;88(5):438–48.
36. Dank JP, Kim S, Parisi MA, et al. Outcome after surgical repair of junctional epidermolysis bullosa-pyloric atresia syndrome: a report of 3 cases and review of the literature. *Arch Dermatol* 1999;135(10):1243–7.
37. Kiritsi D, Has C, Bruckner-Tuderman L. Laminin 332 in junctional epidermolysis bullosa. *Cell Adh Migr* 2013;7(1):135–41.
38. Yuen WY, Lemmink HH, van Dijk-Bos KK, et al. Herlitz junctional epidermolysis bullosa: diagnostic features, mutational profile, incidence and population carrier frequency in the Netherlands. *Br J Dermatol* 2011;165(6):1314–22.
39. Varki R, Sadowski S, Pfendner E, et al. Epidermolysis bullosa. I. Molecular genetics of the junctional and hemidesmosomal variants. *J Med Genet* 2006;43(8):641–52.
40. Pasmooij AM, Pas HH, Jansen GH, et al. Localized and generalized forms of blistering in junctional epidermolysis bullosa due to COL17A1 mutations in the Netherlands. *Br J Dermatol* 2007;156(5):861–70.
41. Kiritsi D, Kern JS, Schumann H, et al. Molecular mechanisms of phenotypic variability in junctional epidermolysis bullosa. *J Med Genet* 2011;48(7):450–7.
42. Pfendner EG, Lucky AW. Epidermolysis bullosa with pyloric atresia. In: Pagon RA, Bird TD, Dolan CR, et al, editors. *Seattle: GeneReviews*; 1993.
43. Dharma B, Moss C, McGrath JA, et al. Dominant dystrophic epidermolysis bullosa presenting as familial nail dystrophy. *Clin Exp Dermatol* 2001;26(1):93–6.
44. Christiano AM, Fine JD, Uitto J. Genetic basis of dominantly inherited transient bullous dermatolysis of the newborn: a splice site mutation in the type VII collagen gene. *J Invest Dermatol* 1997;109(6):811–14.
45. Fassihi H, Diba VC, Wessagowit V, et al. Transient bullous dermatolysis of the newborn in three generations. *Br J Dermatol* 2005;153(5):1058–63.
46. Fine JD, Mellerio JE. Extracutaneous manifestations and complications of inherited epidermolysis bullosa: part II. Other organs. *J Am Acad Dermatol* 2009;61(3):387–402.
47. Wright JT. Oral manifestations in the epidermolysis bullosa spectrum. *Dermatol Clin* 2010;28(1):159–64.
48. Almaani N, Mellerio JE. Genitourinary tract involvement in epidermolysis bullosa. *Dermatol Clin* 2010;28(2):343–6, xi.
49. Haynes L. Nutrition for children with epidermolysis bullosa. *Dermatol Clin* 2010;28(2):289–301.
50. Hubbard L, Haynes L, Sklar M, et al. The challenges of meeting nutritional requirements in children and adults with epidermolysis bullosa: proceedings of a multidisciplinary team study day. *Clin Exp Dermatol* 2011;36(6):579–84.
51. Kuo DJ, Bruckner AL, Jeng MR. Darbepoetin alfa and ferric gluconate ameliorate the anemia

- associated with recessive dystrophic epidermolysis bullosa. *Pediatr Dermatol* 2006;23(6):580–5.
52. Dang N, Murrell DF. Mutation analysis and characterization of COL7A1 mutations in dystrophic epidermolysis bullosa. *Exp Dermatol* 2008;17(7):553–68.
 53. Lai-Cheong JE, McGrath JA. Kindler syndrome. *Dermatol Clin* 2010;28(1):119–24.
 54. D'Souza MA, Kimble RM, McMillan JR. Kindler syndrome pathogenesis and fermitin family homologue 1 (kindlin-1) function. *Dermatol Clin* 2010;28(1):115–18.
 55. Sawardekar SS, Zaenglein AL. Ankyloblepharon-ectodermal dysplasia-clefting syndrome: a novel p63 mutation associated with generalized neonatal erosions. *Pediatr Dermatol* 2011;28(3):313–17.
 56. Pohla-Gubo G, Cepeda-Valdes R, Hintner H. Immunofluorescence mapping for the diagnosis of epidermolysis bullosa. *Dermatol Clin* 2010;28(2):201–10.
 57. Yiasemides E, Walton J, Marr P, et al. A comparative study between transmission electron microscopy and immunofluorescence mapping in the diagnosis of epidermolysis bullosa. *Am J Dermatopathol* 2006;28(5):387–94.
 58. Fassih H, McGrath JA. Prenatal diagnosis of epidermolysis bullosa. *Dermatol Clin* 2010;28(2):231–7, viii.
 59. Bello YM, Falabella AF, Schachner LA. Management of epidermolysis bullosa in infants and children. *Clin Dermatol* 2003;21(4):278–82.
 60. Schachner L, Feiner A, Camisulli S. Epidermolysis bullosa: management principles for the neonate, infant, and young child. *Dermatol Nurs* 2005;17(1):56–9.
 61. Schober-Flores C. Epidermolysis bullosa: the challenges of wound care. *Dermatol Nurs* 2003;15(2):135–8, 41–44.
 62. Weiner MS. Pain management in epidermolysis bullosa: an intractable problem. *Ostomy Wound Manage* 2004;50(8):13–14.
 63. Lara-Corrales I, Arbuckle A, Zarinehbf S, et al. Principles of wound care in patients with epidermolysis bullosa. *Pediatr Dermatol* 2010;27(3):229–37.
 64. Pope E, Lara-Corrales I, Mellerio J, et al. A consensus approach to wound care in epidermolysis bullosa. *J Am Acad Dermatol* 2012;67(5):904–17.
 65. Mellerio JE. Infection and colonization in epidermolysis bullosa. *Dermatol Clin* 2010;28(2):267–9, ix.
 66. Birge K. Nutrition management of patients with epidermolysis bullosa. *J Am Diet Assoc* 1995;95(5):575–9.
 67. Fine JD, Johnson LB, Weiner M, et al. Assessment of mobility, activities and pain in different subtypes of epidermolysis bullosa. *Clin Exp Dermatol* 2004;29(2):122–7.
 68. Goldschneider KR, Lucky AW. Pain management in epidermolysis bullosa. *Dermatol Clin* 2010;28(2):273–82.
 69. Arbuckle HA. Bathing for individuals with epidermolysis bullosa. *Dermatol Clin* 2010;28(2):265–6.
 70. Harrison D, Beggs S, Stevens B. Sucrose for procedural pain management in infants. *Pediatrics* 2012;130(5):918–25.
 71. Marini I, Vecchiet F. Sucralfate: a help during oral management in patients with epidermolysis bullosa. *J Periodontol* 2001;72(5):691–5.
 72. Goldschneider K, Lucky AW, Mellerio JE, et al. Perioperative care of patients with epidermolysis bullosa. *Proceedings of the 5th International Symposium on Epidermolysis Bullosa, Santiago Chile, December 4–6. Paediatr Anaesth* 2010;20(9):797–804.
 73. Nandi R, Howard R. Anesthesia and epidermolysis bullosa. *Dermatol Clin* 2010;28(2):319–24.
 74. Yan EG, Paris JJ, Ahluwalia J, et al. Treatment decision-making for patients with the Herlitz subtype of junctional epidermolysis bullosa. *J Perinatol* 2007;27(5):307–11.
 75. Kramer SM, Serrano MC, Zillmann G, et al. Oral health care for patients with epidermolysis bullosa – best clinical practice guidelines. *Int J Paediatr Dent* 2012;22(Suppl. 1):1–35.
 76. Mavilio F, Pellegrini G, Ferrari S, et al. Correction of junctional epidermolysis bullosa by transplantation of genetically modified epidermal stem cells. *Nat Med* 2006;12(12):1397–402.
 77. Siprashvili Z, Nguyen NT, Bezchinsky MY, et al. Long-term type VII collagen restoration to human epidermolysis bullosa skin tissue. *Hum Gene Ther* 2010;21(10):1299–310.
 78. Wagner JE, Ishida-Yamamoto A, McGrath JA, et al. Bone marrow transplantation for recessive dystrophic epidermolysis bullosa. *N Engl J Med* 2010;363(7):629–39.
 79. Remington J, Wang X, Hou Y, et al. Injection of recombinant human type VII collagen corrects the disease phenotype in a murine model of dystrophic epidermolysis bullosa. *Mol Ther* 2009;17(1):26–33.
 80. Woodley DT, Keene DR, Atha T, et al. Injection of recombinant human type VII collagen restores collagen function in dystrophic epidermolysis bullosa. *Nat Med* 2004;10(7):693–5.
 81. Hup JM, Bruinsma RA, Boersma ER, et al. Neonatal pemphigus vulgaris: transplacental transmission of antibodies. *Pediatr Dermatol* 1986;3(6):468–72.
 82. Panko J, Florell SR, Hadley J, et al. Neonatal pemphigus in an infant born to a mother with serologic evidence of both pemphigus vulgaris and gestational pemphigoid. *J Am Acad Dermatol* 2009;60(6):1057–62.
 83. Bonifazi E, Milioto M, Trashlieva V, et al. Neonatal pemphigus vulgaris passively transmitted from a clinically asymptomatic mother. *J Am Acad Dermatol* 2006;55(Suppl. 5):S113–14.
 84. Hirsch R, Anderson J, Weinberg JM, et al. Neonatal pemphigus foliaceus. *J Am Acad Dermatol* 2003;49(Suppl. 2 Case Reports):S187–9.
 85. Walker DC, Kolar KA, Hebert AA, et al. Neonatal pemphigus foliaceus. *Arch Dermatol* 1995;131(11):1308–11.
 86. Abrams ML, Smidt A, Benjamin L, et al. Congenital epidermolysis bullosa acquisita: vertical transfer of maternal autoantibody from mother to infant. *Arch Dermatol* 2011;147(3):337–41.
 87. Lin MS, Gharia M, Fu CL, et al. Molecular mapping of the major epitopes of BP180 recognized by herpes gestationis autoantibodies. *Clin Immunol* 1999;92(3):285–92.
 88. Aoyama Y, Asai K, Hioki K, et al. Herpes gestationis in a mother and newborn: immunoclinical perspectives based on a weekly follow-up of the enzyme-linked immunosorbent assay index of a bullous pemphigoid antigen noncollagenous domain. *Arch Dermatol* 2007;143(9):1168–72.
 89. Lara-Corrales I, Pope E. Autoimmune blistering diseases in children. *Semin Cutan Med Surg* 2010;29(2):85–91.
 90. Sansaricq F, Stein SL, Petronic-Rosic V. Autoimmune bullous diseases in childhood. *Clin Dermatol* 2012;30(1):114–27.
 91. Hruza LL, Mallory SB, Fitzgibbons J, et al. *Pediatr Dermatol* 1993;10(2):171–6.
 92. Lee SY, Leung CY, Leung CW, et al. Linear IgA bullous dermatosis in a neonate. *Arch Dis Child Fetal Neonatal Ed* 2004;89(3):F280.
 93. Kishida Y, Kameyama J, Nei M, et al. Linear IgA bullous dermatosis of neonatal onset: case report and review of the literature. *Acta Paediatr* 2004;93(6):850–2.
 94. Kanitakis J, Mauduit G, Cozzani E, et al. Linear IgA bullous dermatosis of childhood with autoantibodies to a 230 kDa epidermal antigen. *Pediatr Dermatol* 1994;11(2):139–44.
 95. Julapalli MR, Brandon KL, Rosales CM, et al. Neonatal linear immunoglobulin bullous dermatosis: a rare presentation. *Pediatr Dermatol* 2012;29(5):610–13.
 96. Hamann ID, Hepburn NC, Hunter JA. Chronic bullous dermatosis of childhood: relapse after puberty. *J R Soc Med* 1995;88(5):296P–7P.
 97. Burge S, Wojnarowska F, Marsden A. Chronic bullous dermatosis of childhood persisting into adulthood. *Pediatr Dermatol* 1988;5(4):246–9.
 98. Mintz EM, Morel KD. Clinical features, diagnosis, and pathogenesis of chronic bullous disease of childhood. *Dermatol Clin* 2011;29(3):459–62, ix.
 99. Edwards S, Wojnarowska F, Armstrong LM. Chronic bullous disease of childhood with oral mucosal scarring. *Clin Exp Dermatol* 1991;16(1):41–3.
 100. Marsden RA, McKee PH, Bhogal B, et al. A study of benign chronic bullous dermatosis of childhood and comparison with dermatitis herpetiformis and bullous pemphigoid occurring in childhood. *Clin Exp Dermatol* 1980;5(2):159–76.
 101. Wojnarowska F, Marsden RA, Bhogal B, et al. Chronic bullous disease of childhood, childhood cicatricial pemphigoid, and linear IgA disease of adults. A comparative study demonstrating clinical and immunopathologic overlap. *J Am Acad Dermatol* 1988;19(5 Pt 1):792–805.
 102. Caux F, Kirtschig G, Lemarchand-Venencie F, et al. IgA-epidermolysis bullosa acquisita in a child resulting in blindness. *Br J Dermatol* 1997;137(2):270–5.
 103. Wilson BD, Beutner EH, Kumar V, et al. Linear IgA bullous dermatosis. An immunologically defined disease. *Int J Dermatol* 1985;24(9):569–74.
 104. Eskin-Schwartz M, David M, Mimouni D. Mycophenolate mofetil for the management of autoimmune bullous diseases. *Dermatol Clin* 2011;29(4):555–9.
 105. Eskin-Schwartz M, David M, Mimouni D. Mycophenolate mofetil for the management of autoimmune bullous diseases. *Immunol Allergy Clin North Am* 2012;32(2):309–15, vii.
 106. Chimanovitch I, Hamm H, Georgi M, et al. Bullous pemphigoid of childhood: autoantibodies target the same epitopes within the NC16A domain of BP180 as autoantibodies in bullous pemphigoid of adulthood. *Arch Dermatol* 2000;136(4):527–32.
 107. Singalavanija S, Limpongsanurak W. Immuno-bullous diseases in Thai children: report of 24 cases. *J Med Assoc Thai* 2003;86(Suppl. 3):S681–8.
 108. Waisbourd-Zinman O, Ben-Amitai D, Cohen AD, et al. Bullous pemphigoid in infancy:

- Clinical and epidemiologic characteristics. *J Am Acad Dermatol* 2008;58(1):41–8.
109. Nemeth AJ, Klein AD, Gould EW, et al. Childhood bullous pemphigoid. Clinical and immunologic features, treatment, and prognosis. *Arch Dermatol* 1991;127(3):378–86.
110. Majmudar V, Herath D, O'Toole EA, et al. Bullous pemphigoid of childhood: a rare disease with diagnostic and management challenges. *Clin Exp Dermatol* 2010;35(2):213–14.
111. Levine V, Sanchez M, Nestor M. Localized vulvar pemphigoid in a child misdiagnosed as sexual abuse. *Arch Dermatol* 1992;128(6):804–6.
112. Fisler RE, Saeb M, Liang MG, et al. Childhood bullous pemphigoid: a clinicopathologic study and review of the literature. *Am J Dermatopathol* 2003;25(3):183–9.
113. Kuenzli S, Grimaitre M, Krischer J, et al. Childhood bullous pemphigoid: report of a case with life-threatening course during homeopathy treatment. *Pediatr Dermatol* 2004;21(2):160–3.
114. Martinez-De Pablo MI, Gonzalez-Ensenat MA, Vicente A, et al. Childhood bullous pemphigoid: clinical and immunological findings in a series of 4 cases. *Arch Dermatol* 2007;143(2):215–20.
115. Trueb RM, Didierjean L, Fellas A, et al. Childhood bullous pemphigoid: report of a case with characterization of the targeted antigens. *J Am Acad Dermatol* 1999;40(2 Pt 2):338–44.
116. Fox JC, Kenkare S, Petronic-Rosic V, et al. Bullous pemphigoid in late childhood successfully treated with mycophenolate mofetil as an adjuvant therapy. *Pediatr Dermatol* 2010;27(5):537–9.
117. Marcus KA, Halbertsma FJ, van Steensel MA. A case of juvenile bullous pemphigoid – successful treatment with diaminodiphenylsulfone and prednisone. *Pediatr Dermatol* 2009;26(1):55–8.
118. Toyama T, Nakamura K, Kuramochi A, et al. Two cases of childhood bullous pemphigoid. *Eur J Dermatol* 2009;19(4):368–71.
119. Xiao T, Li B, Wang YK, et al. Childhood bullous pemphigoid treated by i.v. immunoglobulin. *J Dermatol* 2007;34(9):650–3.
120. Arpey CJ, Elewski BE, Moritz DK, et al. Childhood epidermolysis bullosa acquisita. Report of three cases and review of literature. *J Am Acad Dermatol* 1991;24(5 Pt 1):706–14.
121. Yang B, Wang C, Wang N, et al. Childhood epidermolysis bullosa acquisita: report of a Chinese case. *Pediatr Dermatol* 2012;29(5):614–17.
122. Mutasim DF, Cummings MP. Linear IgA disease with clinical and immunopathological features of epidermolysis bullosa acquisita. *Pediatr Dermatol* 1997;14(4):303–6.
123. Bauer JW, Schaeppi H, Metz D, et al. Ocular involvement in IgA-epidermolysis bullosa acquisita. *Br J Dermatol* 1999;141(5):887–92.
124. Tran MM, Anhalt GJ, Barrett T, et al. Childhood IgA-mediated epidermolysis bullosa acquisita responding to mycophenolate mofetil as a corticosteroid-sparing agent. *J Am Acad Dermatol* 2006;54(4):734–6.
125. Wu JJ, Wagner AM. Epidermolysis bullosa acquisita in an 8-year-old girl. *Pediatr Dermatol* 2002;19(4):368–71.
126. Meurer M. Immunosuppressive therapy for autoimmune bullous diseases. *Clin Dermatol* 2012;30(1):78–83.
127. Schiavo AL, Puca RV, Ruocco V, et al. Adjuvant drugs in autoimmune bullous diseases, efficacy versus safety: Facts and controversies. *Clin Dermatol* 2010;28(3):337–43.
128. Nakajima K, Wakiguchi H, Kodama H, et al. Neonatal lupus erythematosus in identical twins, showing transient bullous lesions. *Pediatr Dermatol* 2011;28(4):397–400.
129. Gammon WR, Briggaman RA. Bullous SLE: a phenotypically distinctive but immunologically heterogeneous bullous disorder. *J Invest Dermatol* 1993;100(1):28S–34.
130. Gammon WR, Heise ER, Burke WA, et al. Increased frequency of HLA-DR2 in patients with autoantibodies to epidermolysis bullosa acquisita antigen: evidence that the expression of autoimmunity to type VII collagen is HLA class II allele associated. *J Invest Dermatol* 1988;91(3):228–32.
131. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982;25(11):1271–7.
132. Akoglu G, Erkin G, Cakir B, et al. Cutaneous mastocytosis: demographic aspects and clinical features of 55 patients. *J Eur Acad Dermatol Venereol* 2006;20(8):969–73.
133. Brockow K, Jofer C, Behrendt H, et al. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy* 2008;63(2):226–32.
134. Kiszewski AE, Alvarez-Mendoza A, Rios-Barrera VA, et al. Mastocytosis in children: clinicopathological study based on 35 cases. *Histol Histopathol* 2007;22(5):535–9.
135. Kiszewski AE, Duran-Mckinster C, Orozco-Covarrubias L, et al. Cutaneous mastocytosis in children: a clinical analysis of 71 cases. *J Eur Acad Dermatol Venereol* 2004;18(3):285–90.
136. Walker T, von Komorowski G, Scheurlen W, et al. Neonatal mastocytosis with pachydermic bullous skin without c-Kit 816 mutation. *Dermatology* 2006;212(1):70–2.
137. Lange M, Nidoszytko M, Nidoszytko B, et al. Diffuse cutaneous mastocytosis: analysis of 10 cases and a brief review of the literature. *J Eur Acad Dermatol Venereol* 2012;26(12):1565–71.
138. Koga H, Kokubo T, Akaishi M, et al. Neonatal onset diffuse cutaneous mastocytosis: a case report and review of the literature. *Pediatr Dermatol* 2011;28(5):542–6.
139. DiBacco RS, DeLeo VA. Mastocytosis and the mast cell. *J Am Acad Dermatol* 1982;7(6):709–22.

Introduction

Bacterial skin infections in neonates and infants can present differently from those in older children, based on several factors: (1) the nature of the pathogen; (2) the developmental stage of the infant when infection is acquired: early (first or second trimester) versus late (third trimester) in gestation and early (first few days) versus late (2–8 weeks) postnatal life; and (3) the manner in which inoculation occurs (i.e. vertical transmission in utero, vertical transmission at the time of birth, or postnatally). Infection from hematogenous penetration of the placental barrier or through ruptured amniotic membranes can be more severe and widespread, involving multiple organ systems in addition to the skin, because of the vulnerable state of the developing neonate. Importantly, neonatal cutaneous infections, even those acquired postnatally, are potentially more serious compared with similar cutaneous infections in older children. The reason for these differences in severity is multifactorial, involving a complex interaction between host, pathogen, and environmental factors (Box 12.1).

Furthermore, the potential impact of a localized cutaneous infection is of greater concern in neonates, where alterations of the normal skin barrier are more common and can serve as a conduit for systemic infection. This is especially true for very low-birthweight infants where organisms that normally colonize the skin are also implicated as etiologic agents of sepsis. This suggests that sepsis may be a consequence of bacterial penetration at sites of skin injury or through the immature epidermal barrier.¹ Edwards and colleagues highlighted this concern when they revealed the association of simple bland emollients in very low-birthweight infants with increased risk of neonatal bacterial sepsis caused by normal skin flora.² Given the risk for severe consequences, neonatal cutaneous infections mandate a prompt and thorough evaluation and aggressive treatment to minimize morbidity and mortality.

The clinical presentation, pathogenesis, diagnostic modalities and suggested therapeutic interventions are reviewed for various common and less common neonatal cutaneous infections. The continued emergence of antibiotic resistance has complicated the empiric therapeutic options for some bacterial infections. This emergence of resistance has highlighted the importance of obtaining cultures when possible to identify the pathogen and its sensitivity profile. Recommendations regarding antibiotic choices and duration of therapy specific to the infection are provided for each clinical scenario noting the potential impact of resistance on antibiotic choices.

Superficial infections

IMPETIGO

Impetigo is the single most common primary skin infection in children,³ and impetiginization of atopic dermatitis is the most

important secondary skin infection.⁴ Nonbullous impetigo is a superficial infection localized to the subcorneal portion of the epidermis typically caused *Staphylococcus aureus* and less commonly *Streptococcus pyogenes* (Group A beta-hemolytic streptococci). Bullous impetigo is almost exclusively caused by *Staphylococcus aureus*, most commonly phage group 2 (types 71 and 55) that elaborates toxins.⁵ These toxins cause epidermolysis and subsequent blister formation. Bullous impetigo is thought to be a localized form of staphylococcal scalded skin syndrome (SSSS).⁶

Cutaneous findings

Nonbullous impetigo is characterized by erythematous, honey-colored crusted plaques (Fig. 12.1). Lesions tend to be localized in primary impetigo, but may become more widespread when superimposed on diseased skin (e.g., atopic dermatitis). Moist intertriginous, periorificial and periumbilical areas are commonly involved in both nonbullous and bullous impetigo. Bullous impetigo often presents during the first 2 weeks of life with flaccid, transparent, subcorneal bullae, which may be single or clustered, and often lack underlying cutaneous erythema. The bullae may contain pus that layers out in the dependent portion. The lesions rupture easily, leaving a shallow erosion surrounded by a narrow rim of peeling that heals without scarring (Fig. 12.2). However, postinflammatory pigmentary changes may persist for weeks to months. Multiple small pustules on the abdomen and diaper area are characteristic of staphylococcal pustulosis (Fig. 12.3).⁷ The healing sites from circumcision and the healing umbilical cord can be important niduses of infection in neonates.

Extracutaneous findings

Most cases of impetigo, including neonatal bullous impetigo, are unaccompanied by constitutional signs of illness. Occasionally, hematogenous spread of bacteria can result in osteomyelitis, septic arthritis, pneumonia, or septicemia, particularly in neonates with bullous impetigo.^{3,7}

Etiology and pathogenesis

S. aureus is isolated from approximately 85% of impetigo lesions and in 50–60% of cases is the sole pathogen. *Streptococcus pyogenes* causes the remainder of cases of nonbullous impetigo. The staphylococcal organisms that cause nonbullous impetigo are variable, but are generally not from phage group 2, whereas bullous impetigo is most commonly (80%) the result of *S. aureus* from phage group 2.⁸ Bullae production results from locally produced exfoliative or epidermolytic toxins A or B (ETA and ETB) which cleave desmoglein 1 (DSG1) within desmosomes, via serine proteases.⁹ If there is enough toxin produced, it can disseminate and cleave DSG1 in broader areas, leading to staphylococcal scalded skin syndrome (SSSS, see below). ETA is more commonly associated with bullous



Figure 12.2 Flaccid bullae seen in bullous impetigo that easily rupture, leaving a fine collarette of scale.

BOX 12.1 FACTORS THAT LEAD TO A HIGHER RISK IN NEONATAL INFECTION

- Alterations in or lack of normal bacterial flora
- Predisposing tissue factors, such as local trauma with breach of the epidermal barrier or immature epidermis
- Competence of systemic and local tissue defenses of the host
- Expression of bacterial virulence factors and synergism



Figure 12.1 Honey-colored crusted plaques with a collarette around the edge on the flank of an infant.



Figure 12.3 Multiple vesicles and bullae of staphylococcal pustulosis.

impetigo than is ETB. High titers of neutralizing antibodies against ETA and/or the inability of ETA to penetrate through the epidermis may explain why ETA does not commonly cause SSSS.¹⁰ Methicillin-resistant *Staphylococcus aureus* (MRSA) can cause impetigo, bullous impetigo, orbital cellulitis,¹¹ abscesses, SSSS, necrotizing fasciitis, and toxic shock syndrome that are clinically indistinguishable from similar infections caused by methicillin-sensitive *Staphylococcus aureus* (MSSA).

Diagnosis

As the clinical presentation of MRSA and MSSA bullous impetigo and *S. aureus* and *S. pyogenes* nonbullous impetigo are indistinguishable, obtaining appropriate cultures is imperative to guide therapeutic choices. Culture of fluid from a vesicle, pustule or from beneath the lifted edges of a crusted plaque of impetigo, is usually sufficient to establish a diagnosis. Gram stains can be useful in establishing a rapid presumptive diagnosis but are less sensitive and less specific than a culture. When

the diagnosis is in question, and Gram stain and culture are negative, a skin biopsy can be useful, although this is seldom necessary. When a biopsy is performed, the histopathology often reveals a vesicle or pustule in the subcorneal or granular region of the epidermis with marked dermal inflammation; the cavity is larger in the bullous form.

Differential diagnosis

Staphylococcal impetigo is clinically indistinguishable from streptococcal impetigo unless it is bullous, which is only caused by *Staphylococcus aureus*.³ Impetigo may be confused with several other infectious vesiculobullous or pustular disorders, such as herpes simplex virus (HSV), varicella, enterovirus, congenital cutaneous candidiasis, listeriosis, and scabies, as well as noninfectious disorders such as erythema toxicum neonatorum, transient neonatal pustular melanosis, eosinophilic pustulosis, chronic bullous disease of childhood, incontinentia pigmenti, epidermolysis bullosa, pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid.

Course, management, treatment, and prognosis

For superficial skin infections such as impetigo, the course is often self-limiting. Recently, there has been a trend towards using topical mupirocin, retapamulin (in children over 9 months of age) or fusidic acid (not available in the USA) for localized forms of impetigo and reserving oral antibiotics for those patients with more diffuse involvement or resistant organisms.¹² When systemic antibiotic therapy is deemed necessary, antibiotic coverage should be inclusive of *S. aureus*. Oral antibiotics that are not cleaved by penicillinases present in most *S. aureus* isolates can be effective in this setting. This includes options such as cephalexin, cloxacillin, or dicloxacillin. Each of these options also has the benefit of covering *S. pyogenes* in the setting of nonbullous impetigo. Knowledge of the local epidemiology of MRSA infections is imperative, as a high rate of MRSA would prompt empiric coverage for MRSA in the setting of impetigo. Clindamycin is a reasonable empiric option; however, clindamycin resistance among MSSA and MRSA isolates is also on the rise.¹³

Strains of MRSA have been grouped primarily by the type of resistance genes that they carry in a genetic element referred to as the cassette chromosome element, called SCCmec (SCCmec). Nosocomial MRSA contains types 1, 2, and 3 SCCmec, conferring multidrug resistance to non- β -lactam antibiotics. Community-acquired MRSA contains types 4 or 5 SCCmec, making this strain more susceptible to antimicrobial agents.^{14,15}

There are a number of additional second-line oral agents that may be considered for the treatment of uncomplicated impetigo including cefadroxil, cefprozil, loracarbef, and amoxicillin/clavulanate. It should be noted that none of these second-line agents is effective against MRSA. The changing landscape of resistance necessitates that cultures be performed in order to guide appropriate therapeutic decisions.¹⁶ For isolates that are both MRSA and clindamycin resistant, trimethoprim-sulfamethoxazole may be an effective oral option but should not be used in children under 2 months of age, due to risk of hyperbilirubinemia and kernicterus. Additionally, the clinician should note that trimethoprim-sulfamethoxazole may not adequately cover *Streptococcus pyogenes*.

Various clinical scenarios of skin bacterial infection warrant the use of parenteral therapy. These include: infants presenting

with deeper infections such as furuncles, abscesses, cellulitis, osteomyelitis, endocarditis, and pneumonia. Additionally, as bullous impetigo in neonates may advance rapidly, systemic enteral or parenteral therapy (instead of topical) with close clinical follow-up is encouraged.¹⁷ As with oral therapy, initial empiric parenteral therapy should be guided by local resistance patterns. Regions with low rates of MRSA can employ oxacillin or nafcillin as a first line agent. Those areas with higher rates of MRSA should use clindamycin or vancomycin empirically. Clindamycin, a protein synthesis inhibitor, may be advantageous for decreasing epidermolytic toxin production and is often used as an adjunctive agent in SSSS caused by MSSA or MRSA. Linezolid also shows excellent activity against MRSA and can be considered as an alternative parenteral option. The mortality rate in NICUs due to MRSA infection has been as high as 38% in some cohorts.¹⁸ Mortality rates are highest in infants developing bacteremia and septic shock.^{14,15,18} Late-onset neonatal sepsis, occurring 2–3 weeks after birth, has been seen with nosocomial MRSA infections. Thus, patients should be followed closely, even if they appear healthy.

Once signs of infection have begun to subside, and if constitutional signs are absent, therapy may be completed orally. Duration of therapy should be dictated by the clinical scenario as well as any associated complications. For uncomplicated impetigo, a 7-day course of therapy is typically sufficient. Secondary complications such as bacteremia, osteomyelitis and endocarditis warrant longer parenteral therapeutic courses, which should be managed with consultation from an infectious disease specialist.

INTERTRIGO

Intertrigo is an acute inflammation in a skin fold that can be irritant or infectious in etiology. Neonates and infants have abundant subcutaneous tissue and are often not mobile enough to allow the folds to air out. This occluded skin (neck, axillae and inguinal folds) is prone to overgrowth of yeast and bacteria. Clinicians often overlook staphylococcal and streptococcal infections as important and potentially dangerous causes of intertrigo.

Cutaneous findings

Bacterial intertrigo typically presents with red, slightly eroded, tender, shiny exudative patches centered on a skin fold (Figs 12.4, 12.5). Although the inguinal areas are most common, infants and neonates have many occluded skin folds due to their body habitus (including neck, axillae, antecubital and popliteal fossae) and any of these can become infected. The perianal area can be the initial source of infection and will also have a bright red, eroded appearance when infected with *Strep. pyogenes* or *S. aureus*. Intertrigo can also be present in several skin folds.^{19,20}

Extracutaneous findings

Intertrigo is typically not associated with fever or extracutaneous spread. Untreated streptococcal disease can lead to post-streptococcal glomerulonephritis. Cutaneous streptococcal infections have also been associated with the subsequent development of psoriasis. Specifically, guttate psoriasis or napkin/perineal psoriasis should prompt an evaluation for perianal streptococcal infection in infants.²¹



Figure 12.4 Streptococcal intertrigo: red shiny patches in the popliteal fossa and proximal skin fold caused by *S. pyogenes*.



Figure 12.5 Bright red eroded patch of streptococcal intertrigo. (Courtesy of Alfie Krol, MD.)

Etiology and pathogenesis

Bacterial intertrigo and perianal infection is most commonly due to *Strep. pyogenes* but *S. aureus* (including MRSA) is becoming increasingly recognized as an etiologic pathogen for intertrigo.^{22,23} *Pseudomonas* species are less common causes of intertrigo and are more commonly indicative of a polymicrobial infection.

Differential diagnosis

Intertrigo can be due to irritation from over-washing or use of baby wipes. Seborrheic dermatitis, atopic dermatitis and contact dermatitis can also present with red patches in skin folds and each can become superinfected with bacteria or yeast. Candidal yeast infections often infect skin folds and present with peeling and satellite pustules.

Diagnosis

Although the clinical presentation is often enough to make the diagnosis, a Gram stain and culture from the most eroded or purulent area can be helpful in defining the causative pathogen. However, the results of these cultures need to be interpreted

with the understanding that typical colonizing organisms, especially *S. aureus*, may not represent true infection. Although a rapid *Strep* test may be positive in streptococcal perianal dermatitis, this test has not been approved for use on non-posterior pharyngeal specimens. Potassium hydroxide scrapings and fungal cultures can help diagnose yeast infections.

Course, management, treatment, and prognosis

Intertrigo is worsened by skin occlusion, so allowing the area to aerate is important. Therapy with topical antibiotics such as mupirocin for *S. aureus* or *Strep. pyogenes* or bacitracin-polymyxin B for *Pseudomonas* spp. is often effective. For premature or immunosuppressed infants, or for multifocal and/or complicated infections, systemic therapy may be necessary. A similar approach, as described above for impetigo, should be employed when choosing an oral or parenteral therapeutic agent for intertrigo. A Gram stain and culture of the affected area should be taken before initiating empiric systemic antibiotics. If the culture results suggest a polymicrobial infection or a *Pseudomonas* spp. infection and the clinical scenario requires systemic therapy, then additional input from an infectious disease specialist should be considered.

FOLLICULITIS/PUSTULOSIS/FURUNCULOSIS

Pustules in the neonate or infant can be benign but must be differentiated from infectious pustulosis (bacterial, yeast, herpetic). Bacterial folliculitis is a superficial infection of the hair follicle ostium. Noninfectious pustulosis such as erythema toxicum neonatorum and transient neonatal pustular melanosis are addressed elsewhere in this book but typically are differentiated by their clinical presentation, including time course and superficial nature.

Cutaneous findings

Folliculitis presents as discrete, dome-shaped pustules with an erythematous base located at the ostia of the pilosebaceous canals. The lesions are usually asymptomatic, but may be pruritic or painful. Occasionally, a lesion may extend to involve deeper tissues and form an abscess (e.g., furuncle, carbuncle).

Extracutaneous findings

Extracutaneous findings are not typically present. Rarely, the local infection can progress to a systemic illness that is evident by fever onset and an ill-appearing child.

Etiology and pathogenesis

Folliculitis is caused predominantly by *S. aureus*, although coagulase-negative staphylococci are occasionally involved. A moist environment, maceration, poor hygiene, application of an occlusive emollient, and drainage from adjacent wounds and abscesses can be provoking factors. *Pseudomonas aeruginosa* is a rare cause of folliculitis in infants. It is found in circulating water, and the bacteria become trapped under the clothing, leading to infection. If pustulosis is due to *P. aeruginosa* it is often concentrated in areas that are covered by swimming suits or occluded such as axillae, inguinal folds and trunk.²⁴

Diagnosis

The causative organism of folliculitis can be identified by Gram stain and culture of purulent material from the follicular orifice.

Differential diagnosis

Benign pustulosis of infancy is often on the differential of staphylococcal pustulosis in the neonate. Erythema toxicum neonatorum tends to be more transient and have a splotchy patch of erythema around fragile superficial pustules and the pustule contents contain eosinophils. Transient neonatal pustular melanosis is typically present at birth and the pustules rupture easily and are gone within hours to days; the pustules contain neutrophils similar to bacterial folliculitis but a Gram stain should be negative (although Gram stains have a significant false-negative rate in bacterial infection). *Candida* species, *Pityrosporum ovale*, and *Malassezia furfur* are all yeast pathogens capable of causing follicular papules and/or pustules. Identification of these fungal organisms can be made by potassium hydroxide examination of lesion scrapings or by skin biopsy. Several other conditions may mimic folliculitis, including miliaria, eosinophilic pustular folliculitis, acne neonatorum, tinea corporis, congenital cutaneous candidiasis, scabies, and erythema toxicum neonatorum.

Course, management, treatment, and prognosis

An attempt should be made to identify and eliminate predisposing factors. Localized uncomplicated folliculitis may be managed by removing causative factors, antiseptic cleansing (e.g., chlorhexidine in children over 2 months), and topical antibiotics. Severe or refractory folliculitis should be managed with oral therapy. Similar to impetigo and intertrigo, bacterial Gram stain and culture can be extremely useful to guide appropriate therapy. Initial empiric therapy should be directed at *S. aureus*. In areas with limited MRSA rates, cephalexin, cloxacillin or dicloxacillin are reasonable first-line agents. For regions where MRSA prevalence is higher, initial empiric therapy with clindamycin should be considered. Neonates and immunosuppressed infants may require intravenous therapy. Recurrent episodes should warrant investigation into asymptomatic nasal carriage of *S. aureus* by the patient, immediate caregivers, pets or other contaminated objects in the child's environment.²⁵ Decolonizing efforts including intranasal mupirocin and antibacterial washes should be considered for direct caretakers of infected infants, especially if the infection is recurrent.

Infection of pre-existing erosions and ulcerations

Open wounds that are not initially caused by a bacterial infection, such as those caused by epidermolysis bullosa (EB), autoimmune blistering diseases, ulcerated hemangiomas or vesicular infections (herpes simplex or varicella) often become colonized with bacteria but can also become secondarily infected. It is important for the clinician to be able to differentiate colonization from infection to determine if antibiotics are necessary.

Cutaneous findings

Erosions and ulcerations that are secondarily infected can present with a myriad of symptoms that include purulent drainage, crusting, erythema expanding from the wound, pain, and acute worsening that cannot be explained by the primary process. Green discharge or discoloration on dressings may be a marker of *Pseudomonas* infection.

Extracutaneous findings

Sepsis can occur secondary to bacterial infection of pre-existing erosions or ulcerations leading to fever, hypotension and potentially death. Sepsis complicating varicella-related skin ulcerations has been reported secondary to Gram-positive organisms including *S. aureus* and *Strep. pyogenes*, as well as Gram-negative pathogens such as *Pseudomonas* spp. and *Escherichia coli*.²⁶

Etiology and pathogenesis

Cutaneous ulcerations are most typically colonized with normal skin flora such as diphtheroids, coagulase-negative staphylococci or anaerobes (especially in the perineum). *S. aureus*, streptococci (especially *S. pyogenes*) and *Pseudomonas* can also flourish in open wounds and are more pathogenic. The open wound lacks the physical protection of the epidermis and creates a warm, moist environment for bacterial overgrowth.

Diagnosis

Clinical interpretation of the likelihood of infection versus colonization is important but if infection is suspected, the wound should be cultured. The amount of bacteria, rapidity of bacterial growth in culture and the presence of just one pathogenic bacteria that has outcompeted the normal skin flora all suggest a true infection versus colonization.

Differential diagnosis

Ulcers can acutely worsen and drain due to the primary disease process, such as in pyoderma gangrenosum. Herpetic infections as well as yeast infections such as those caused by *Candida* spp. can also superinfect open wounds.

Course, management, treatment, and prognosis

Infected ulcers and erosions will often fail to heal at the same rate as the non-infected ulcers or erosions. Untreated, the areas may never heal, and may progress to cellulitis or systemic infection. Some erosions or ulceration in patients with EB are chronically colonized and so therapy should only be started if there is a clinical change or an area that is determined not to heal because of secondary infection. Topical therapy (such as mupirocin or bacitracin-polymyxin B) is often enough for localized areas. Metronidazole is often used for ulceration of perineal hemangiomas in order to cover anaerobic gut flora.²⁷ Anecdotally, patients with chronic wounds such as those with EB will often rotate the type of topical antibiotic they use so as not to induce resistance. Systemic therapy should be reserved for patients with widespread infection, cellulitis or worsening infection, despite adequate topical therapy. As has been noted previously, therapy should be guided by the results of bacterial cultures. Initial empiric therapy should be directed at Gram-positive organisms with cephalexin, cloxacillin, dicloxacillin, or clindamycin. Infection secondary to *S. pyogenes* should always dictate systemic antibiotic therapy because of its potential for causing glomerulonephritis. Although less frequent, Gram-negative pathogens are possible and thus expanding antibiotic coverage for such pathogens should be considered if the clinical scenario is worsening, despite Gram-positive coverage, or if culture results suggest a Gram-negative pathogen.

PARONYCHIA

Paronychia is a localized inflammation of the nail fold, which is usually acquired, rather than congenital and can be either



Figure 12.6 Paronychia, presenting with erythema and edema of the lateral nail fold, due to *Staphylococcus aureus* in this case.

acute or chronic.²⁸ Bacterial paronychia typically presents with the lateral nail fold becoming warm, erythematous, edematous, and painful (Fig. 12.6). A purulent exudate may develop. Dermatitis and loss of the cuticle in the affected area may contribute to initiation and/or perpetuation of the problem.

Although the primary disorder is separation of the eponychium from the nail plate, secondary infection is common. *S. aureus* and *Strep. pyogenes* are the most common aerobic organisms. Occasionally, Gram-negative organisms such as *Pseudomonas* spp., *Proteus* spp., and *E. coli* are involved.²⁹ Paronychia is often associated with thumb-sucking.

The diagnosis is usually made clinically; in selected cases both aerobic and anaerobic cultures of purulent material may be useful in directing appropriate therapy.

The differential diagnosis includes *Candida* spp. infection, a frequent cause of acute and chronic paronychia in neonates, herpetic whitlow, and atopic dermatitis. Treatment includes measures directed at eliminating or reducing predisposing factors of nail-fold maceration and trauma (such as thumb-sucking). Warm compresses generally are curative for superficial lesions. Drainage of the abscess may be facilitated by gently pushing the nail fold away from the nail plate. In addition to incision and drainage, antibiotics are needed for treatment of deeper lesions. Dicloxacillin, cloxacillin, cephalexin or clindamycin (if MRSA is prevalent in the locality) are the antibiotics of choice for treatment of infections caused by *S. aureus*, whereas amoxicillin plus clavulanic acid is preferred for empiric treatment when additional anti-anaerobic therapy is desired. Concomitant *Candida albicans* can be present requiring topical or systemic anti-fungal therapy.

FUNISITIS/OMPHALITIS

Funisitis is inflammation of the umbilical cord characterized by increased secretions and a foul odor. Funisitis may accompany chorioamnionitis. Omphalitis is an infection of the umbilical stump. Low-birthweight infants and those with complicated deliveries are at increased risk for omphalitis.³⁰

Cutaneous findings

Excessive exudate from the umbilical stump, as seen in funisitis, may be a harbinger of subsequent infection. The exudate may be accompanied by bleeding from the umbilical vessels caused by a delay in closure. Omphalitis shows periumbilical erythema, edema, and tenderness, with or without discharge. Typically, signs of infection occur on the third day of life. The infection may extend subcutaneously to cause cellulitis, or along abdominal wall fascial planes leading to necrotizing fasciitis. Black discoloration or crepitus of the periumbilical tissues suggests more advanced infection.

Extracutaneous findings

The umbilical cord of the newborn infant is a particularly common portal of entry for invasive bacterial pathogens. Invasion may occur directly into the peritoneal cavity, with resultant peritonitis. Ascending infection along the umbilical vein is a particularly serious complication. Septic umbilical arteritis or suppurative thrombophlebitis of umbilical or portal veins, portal vein thrombosis, and liver abscesses may occur. Septic embolization from infected umbilical vessels (arteries or the vein) is uncommon, but may seed various organs, including the lungs, pancreas, kidneys, liver, brain, heart (i.e., endocarditis), or skin.

Etiology and pathogenesis

The umbilical cord stump may become highly colonized with pathogenic bacteria shortly after birth, including the mother's vaginal and skin flora and bacteria from the hands of caregivers, including healthcare workers. Omphalitis is caused by a variety of these colonizing organisms, but *S. aureus* and Gram-negative organisms are most common, while anaerobes are an infrequent cause.^{31,32} Candidal funisitis has also been reported.³³

Diagnostics

Gram stain and culture of moist umbilical cord or stump material may show organisms and be helpful in the early diagnosis and therapeutic decision process for funisitis or omphalitis. As with all cutaneous infections, the results of Gram stain and culture must be interpreted along with clinical signs to determine true infection as cultures will likely yield colonizing organisms, even in the absence of infection.

Differential diagnosis

The serous secretions of funisitis/omphalitis must be distinguished from those of a vitelline duct remnant, umbilical papilloma, or urachal remnant. Inflammatory disorders, such as seborrheic dermatitis and psoriasis, can affect the umbilical region.

Course, management, treatment, and prognosis

As progression to severe sequelae is a major concern, patients should be initiated on parenteral broad-spectrum antibiotics directed against Gram-positive and Gram-negative organisms.³⁴ Definitive recommendations on empiric therapeutic choices are difficult owing to the variation in regional resistance rates. Empiric therapy should be dictated by each institution's local resistance profile for *S. aureus* and Gram-negative organisms. Ampicillin-sulbactam is a reasonable empiric therapeutic option but if MRSA is a concern, the combination of clindamycin or vancomycin and gentamicin would be reasonable. In an infant who is ill-appearing, broadening coverage to include vancomycin, a higher generation cephalosporin and metronidazole may be warranted. Intravenous antibiotics should be continued until the erythema and drainage subside. Complications include evisceration, umbilical hernia, necrotizing fasciitis, cellulitis, peritonitis, superficial abscess, liver abscess and peritoneal adhesions.³⁵ Predictors of poor outcome include early onset of the infection, unplanned home delivery, and temperature instability. Patients should be monitored closely for signs of necrotizing fasciitis, which has a high mortality rate.



Figure 12.7 Red edematous warm patch of cellulitis. (Courtesy of Antonio Torrelo, MD.)

CELLULITIS

Cellulitis is characterized by infection of the dermis and subcutaneous tissues with relative sparing of the epidermis. A break in the skin resulting from trauma, surgery, or an underlying skin lesion predisposes to cellulitis. Cellulitis may be seen more commonly in patients predisposed to abnormal lymphatic drainage (e.g., Klippel–Trenaunay syndrome and lymphatic malformations) as well as in immunodeficiency disorders, but also can occur in otherwise healthy infants.

Cutaneous findings

Cellulitis presents as an area of edema, warmth, erythema, and tenderness (Fig. 12.7). The lateral margins tend to be indistinct because the process is deep in the skin. Application of pressure may produce pitting and pain. Cellulitis caused by *S. aureus* tends to be more localized and may be suppurative. Erysipelas is a superficial infection of the lymphatics typically caused by *S. pyogenes* that presents with bright red patches that tend to spread more rapidly and is often quite tender to palpation. There is often some break in the skin that is a portal of entry for the bacteria, leading to infection.

Extracutaneous findings

Regional adenopathy and constitutional signs and symptoms of fever, chills, and malaise are common. Complications of cellulitis include bacteremia with additional sequelae such as osteomyelitis, septic arthritis, and thrombophlebitis. Glomerulonephritis also can follow infection with *S. pyogenes*.

Etiology and pathogenesis

Besides *S. aureus* and *Strep. pyogenes*, group B streptococci are of major concern in the neonatal period. Additionally, *Streptococcus pneumoniae*, group G or C streptococci and Gram-negative agents, such as *E. coli*, have been implicated in cellulitis. In premature newborns, or newborns with immunologic defects, a number of other bacterial or fungal organisms need to be considered. *Pasteurella multocida* is implicated in cellulitis that follows dog or cat bites, whereas human bites may become infected with *Eikenella corrodens*. Immunization against *Haemophilus influenzae* type B has significantly reduced the incidence of cellulitis due to this organism.³⁶

Diagnostics

Although not routinely necessary, aspirates from the leading edge of inflammation, skin biopsy, and blood cultures

collectively allow for identification of the causal organism in approximately 25% of cellulitis cases. Importantly, an aspirate taken from the point of maximum inflammation yields the causal organism more often than does a leading-edge aspirate, and thus this approach may be favored.³⁷ Lack of success in isolating an organism stems primarily from the low number of organisms present within the lesion.

Differential diagnosis

Wells syndrome, insect bites, drug reactions, contact dermatitis, subcutaneous fat necrosis, and cold panniculitis may resemble cellulitis.

Course, management, treatment, and prognosis

Empiric therapy for cellulitis should be directed by the history of the illness, the location and character of the cellulitis, and the age and immune status of the patient. Cellulitis in the neonate should prompt a sepsis workup, followed by initiation of empiric therapy intravenously with a penicillinase-stable antistaphylococcal antibiotic such as cefazolin, oxacillin, or nafcillin, and an aminoglycoside such as gentamicin or a cephalosporin such as cefotaxime. In areas with a high prevalence of MRSA, clindamycin or, if the child is severely ill, vancomycin should be considered. Once the regional erythema, warmth, edema, and fever have decreased significantly, transition to an oral regimen for completion in the outpatient setting is reasonable, provided that other sites of infection (e.g., the CSF) have been excluded.

PERIORBITAL/ORBITAL CELLULITIS

Infection of the soft tissues surrounding the eye is classified as periorbital (preseptal) cellulitis or orbital (postseptal) cellulitis.

Cutaneous findings

The orbital septum connects the orbital periosteum to the upper and lower eyelid structures. This tough fibrous band acts to prevent superficial infections from extending into the orbit and threatening vision. Periorbital cellulitis is a superficial infection that presents with redness, swelling, and tenderness of soft tissues anterior to the orbital septum. Orbital cellulitis involves deeper structures behind the orbital septum. Orbital cellulitis can be associated with sinusitis or direct penetrating trauma to the orbital septum. Orbital cellulitis presents with eyelid erythema, edema, and conjunctival hyperemia, and is distinguished clinically from periorbital cellulitis by ocular involvement.

Extracutaneous findings

Periorbital cellulitis can be associated with bacteremia, particularly when *Streptococcus pneumoniae* is involved. Orbital cellulitis is associated with proptosis, limited painful eye movement, decreased vision, and loss of corneal sensation. Constitutional signs such as fever can be seen with both periorbital and orbital cellulitis.

Etiology and pathogenesis

As noted above, periorbital cellulitis is a superficial infection and as such is more frequently caused by skin colonizers such as *Staphylococcus* spp. and *Streptococcus* spp.³⁸ Orbital cellulitis is most commonly caused by an extension of ethmoiditis into the surrounding soft tissue. Although other sinus pathogens are

linked to orbital cellulitis in children, *S. aureus* and, less commonly, *Strep. pneumoniae* are the more common pathogens described in neonatal orbital cellulitis.^{22,39} MRSA has less commonly been associated with orbital cellulitis in newborns^{23,24}; however, with the recent increase in MRSA, it is likely that the frequency of neonatal orbital cellulitis caused by MRSA will also continue to increase.⁴⁰

Diagnosis

As the landscape of antibiotic resistance changes, surgical intervention for drainage and attainment of cultures, if possible, can be extremely helpful in guiding antibiotic therapy choices. Positive blood cultures can be helpful in directing therapy but they are positive in a minority of cases. Ultrasound cannot reliably detect deep soft tissue infection; therefore, computed tomography (CT) is the most appropriate imaging study to define the extent of infection. Prompt imaging should be undertaken in any infant with proptosis and limited eye movement, as a delay in diagnosing orbital cellulitis can threaten vision and result in death.⁴¹

Differential diagnosis

Adenoviral conjunctivitis may mimic preseptal and septal cellulitis. Orbital pseudotumor, rhabdomyosarcoma, and *Aspergillus* fungal sinusitis must be excluded in the patient with periorbital swelling. A stye, or insect bite, can cause localized redness and edema in the eyelid, mimicking preseptal cellulitis but typically, there is a lack of fever, pain and constitutional symptoms.

Course, management, treatment, and prognosis

Deep soft tissue infection in the orbital region is a medical emergency. Making definitive recommendations on empiric antibiotic therapy for neonatal periorbital and orbital cellulitis is challenging. Clinicians need to be aware that the epidemiology of pathogens causing neonatal orbital cellulitis differs from that of older children.⁴² Generally speaking, antibiotic therapy should be directed at *S. aureus* and *Strep. pneumoniae* with less concern for anaerobes and other sinus commensals. In regions where MRSA rates are high, initial Gram-positive coverage should be broadened to include MRSA. Most pain can be managed adequately with decongestants and analgesics. Prompt consultation with ophthalmology and otorhinolaryngology should be obtained. Signs of optic nerve compression, such as decreased visual acuity, require urgent surgical decompression of the orbital space and infected sinuses.²⁴ Transition to oral therapy can be considered once source control is established and clinical improvement has been shown to be robust. Although the most appropriate duration of therapy is not well studied, most experts continue therapy for 2–3 weeks.⁴³

Subcutaneous and systemic infections

ABSCESSSES

An abscess is a localized collection of pus in a cavity formed by the disintegration or necrosis of tissue, resulting in a firm, tender, erythematous nodule that becomes fluctuant (Figs 12.8, 12.9). In the neonatal period, an abscess is a potentially serious infection because of the higher risk for bacterial dissemination. Specific scenarios of breast and scalp abscesses are discussed below.



Figure 12.8 Cellulitis and underlying abscess in a neonate. In this case the abscess was due to an intravenous line. 'Inking' the margin, as was done in this case, is one way to determine response to treatment.

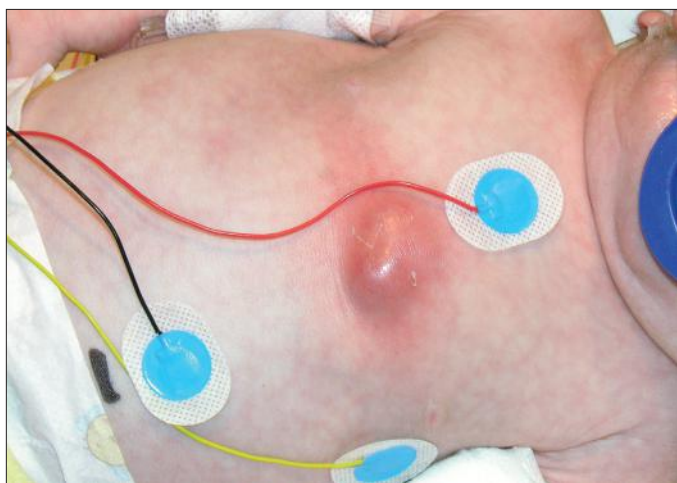


Figure 12.9 Red tender staphylococcal abscess in an infant. (Courtesy of Antonio Torrelo, MD.)

Cutaneous findings

Abscesses present with erythema, induration and pain to palpation. Depending on their depth and amount of time present, they may have fluctuance, or a pustule on top or drain to the surface.

Extracutaneous findings

Most localized furuncles are not associated with systemic findings. However, infants with an abscess should be closely monitored for signs and symptoms of bacterial sepsis, including temperature instability, irritability, poor oral intake, and leukocytosis ($>15\,000/\text{mm}^3$). Bacteremia can lead to hematogenous spread of the pathogen to other viscera and bones.

Etiology and pathogenesis

S. aureus is the single most common pathogen causing abscesses but *Strep. pyogenes* is found commonly as well. MRSA sometimes has virulence factors making infections caused by MRSA more likely to lead to abscess or furuncle formation. Abscesses can be seen in normal newborns, but multiple abscesses are characteristic of immunodeficiency syndromes, such as hyper-IgE syndrome and leukocyte adhesion deficiency.

Although *S. aureus* dominates as the causative pathogen of skin abscesses, other pathogens are possible. Prior to routine

vaccination, *Haemophilus influenzae* type B was a well-documented cause of head and neck abscesses. In the setting of perianal and perineal abscesses, aerobic and anaerobic flora from the gastrointestinal and urinary tract should be considered. *Neisseria gonorrhoeae* has even been identified as the source of an abdominal abscess in a child.⁴⁴ Identification of organisms not typically associated with abscess formation, especially organisms of low virulence, should raise concerns about underlying immunodeficiency.

Diagnosis

An abscess is typically a clinical diagnosis based on warmth, redness, induration, as well as pain and fluctuance on palpation. If the diagnosis is in question, an ultrasound can be useful to establish the presence of, size, and extent of any pocket of purulence. The therapy is to incise and drain amenable lesions; and the process of draining fluid also confirms the diagnosis of an abscess. Additional diagnostic testing such as blood cultures should be performed on a case-by-case basis. Recent data suggest that blood cultures in afebrile neonates with skin and soft tissue infections, including abscesses, are unnecessary.⁴⁵ However, in febrile patients, blood cultures should be performed routinely. Additionally, blood cultures should be considered for premature and very low-birthweight infants as well as any child who is immunosuppressed.

Course, management, treatment, and prognosis

Incision and drainage is the treatment of choice for localized, uncomplicated abscesses in full-term neonates and infants who are otherwise well. Appropriate cultures should always be ordered for bacterial identification and sensitivities. The need for additional antibiotic coverage in the well-appearing neonate with adequate source control is not clear. Studies in children 6 months of age and older have shown that adequate drainage of an uncomplicated skin and soft tissue infection without subsequent administration of an antibiotic active against the identified pathogen is an effective approach.⁴⁶ Although this study did not include those less than 6 months of age, it is reasonable to consider a similar approach assuming that close follow-up can be established. However, for premature, very low-birthweight or immunosuppressed neonates, intravenous antibiotics with MRSA coverage should be initiated (vancomycin or clindamycin typically); and an appropriate systemic workup should be done, including blood cultures.⁴⁷

There are a few locations of abscesses in neonates and infants that have unique clinical diagnostic and therapeutic implications and are presented separately.

BREAST ABSCESS

Breast abscesses develop in full-term neonates during the first 1–6 weeks of life, most commonly during the 4th and 5th weeks.⁴⁸ The incidence is approximately equal in males and females during the first 2 weeks of life, but thereafter, the incidence in girls is nearly twice that in boys.

Cutaneous findings

Breast abscesses present initially with breast enlargement, accompanied by varying degrees of erythema, induration, and tenderness. Fluctuance may or may not occur, depending in part on how early antibiotic therapy is initiated. Bilateral

infection occurs in less than 5% of cases. Breast abscesses caused by *S. aureus* are accompanied by cutaneous pustules or bullae on the trunk, particularly in the perineal region, in 25–50% of patients. The symptoms, age at presentation, and clinical findings of infants with breast abscess caused by Gram-negative bacilli or anaerobes, are similar to those of infants infected with *S. aureus*. A noted exception is for infants infected with *Salmonella* species; they generally also have gastrointestinal illness.

Extracutaneous findings

A minority of patients develop fever (approx. one-third) and constitutional symptoms, such as irritability or toxicity, are uncommon. Leukocytosis ($>15\,000/\text{mm}^3$) is found in approximately half to two-thirds of patients. Concomitant bacteremia, pneumonia, osteomyelitis, or sepsis is unusual.

Etiology and pathogenesis

Breast abscess is usually due to *S. aureus*, but occasionally is caused by group B streptococci, *E. coli*, *Salmonella* spp., *Proteus mirabilis*, *Pseudomonas aeruginosa*, or *Ureaplasma urealyticum*.⁴⁹ Although anaerobic organisms can be isolated from up to 40% of infections, their pathogenic role in neonates is questionable, and therapy directed specifically against them is generally unnecessary. The increased incidence in girls after 2 weeks of age (when breast gland development is more pronounced in girls than boys) and the lack of the disorder in the underdeveloped breast of premature infants, suggest that increased ductal tissue may be a factor in pathogenesis. Breast manipulation has also been suggested as a predisposing factor. Infants with *S. aureus* breast abscesses are typically colonized with the same organism in the nose or pharynx. It seems likely that *S. aureus* colonizing the skin of the nipple subsequently tracks up the ducts of the physiologically enlarged, predisposed breast, perhaps facilitated by breast manipulation, to infect deeper tissues.

Diagnosis

Gram stain of material expressed from the nipple or obtained by needle aspiration or incision and drainage can help identify the organism and guide initial antibiotic therapy. The presence of accompanying cutaneous vesicles or bullae may help in identifying *S. aureus* as the causal agent.

Course, management, treatment, and prognosis

Typically, breast abscesses remain localized and resolve with appropriate therapy. If fluctuance is absent, systemic antibiotic therapy may be curative and prevent abscess development. If fluctuance is present, the abscess must be drained by needle aspiration, by gently expressing pus from the nipple, or surgically, and Gram stain and culture obtained. Data in older children suggest that breast abscesses often result in the need for hospital admission.⁵⁰ Although fewer data exist relative to neonatal breast abscesses, it is prudent to admit patients for parenteral antibiotic therapy. Antibiotics directed against *S. aureus* should be initiated as primary therapy. If local resistant patterns denote high rates of MRSA, then an agent such as vancomycin or clindamycin should be started. Blood cultures have been recommended in this clinical scenario, however the clinical impact of such testing has not been established.⁵¹ If the infant is displaying other concerning symptoms such as fever, or is ill-appearing, cultures of blood, urine and CSF should be considered. If Gram-negative bacilli are seen on the Gram stain,

initial therapy should include Gram-negative coverage with an aminoglycoside or cefotaxime, while awaiting culture results. Once the infection has begun to subside, transition to oral therapy may be considered. In most instances, a total of 5–7 days of therapy is sufficient, although many experts continue treatment for 10–14 days. The most common complication of breast abscess is cellulitis, which develops in approximately 5–10% of affected infants. The cellulitis is generally localized, but can extend rapidly to involve the shoulder and/or abdomen. Scar formation leading to decreased breast size following puberty can occur as a late complication.

SCALP ABSCESS

Scalp abscesses can develop in neonates at the insertion site of a fetal scalp monitoring electrode or because of local perinatal trauma to the scalp. The reported incidence of scalp abscess in neonates who undergo fetal scalp monitoring is between 0.1% and 5.2%.⁵²

Cutaneous findings

Presentation occurs most commonly on day 3 or 4 of life, but may be as early as the first day and as late as 3 weeks. The lesion initially appears as a localized, erythematous area of induration, 0.5–2 cm in diameter. The site may become fluctuant or pustular.

Extracutaneous findings

Regional lymphadenopathy may be present, but other more serious complications, such as cranial osteomyelitis, subgaleal abscess, necrotizing fasciitis of the scalp, bacteremia, sepsis, and death, are rare.

Etiology and pathogenesis

Scalp abscesses are typically polymicrobial, including both aerobes and anaerobes. The anaerobic flora present reflect those found in the normal cervix during labor. The most common pathogenic organisms are *Streptococcus* spp. and *E. coli*.⁵³ The most plausible hypothesis for the pathogenesis of scalp abscess is that the infection occurs via the ascent of normal cervical flora into the uterus following rupture of membranes, aided by procedures that access the uterine cavity. Placement of the electrode breaks the skin barrier, providing a foreign-body nidus for infection in the subcutaneous tissue. Risk factors include longer duration of ruptured membranes, longer duration of monitoring, monitoring for high-risk indications, amnionitis, and endometritis. In general, it appears that procedures that serve to provide increased access of vaginal flora to the infant, or more trauma to the scalp, may increase the risk of abscess development.

Diagnosis

Infants who are subjected to scalp electrode monitoring in utero should be followed closely during the first weeks of life for evidence of infection. If infection is suspected, culture for both aerobic and anaerobic organisms can be obtained ideally by needle aspiration or less ideally by swabbing the exudate expressed from the puncture site.

Differential diagnosis

The differential diagnosis includes cephalohematoma and HSV infection. A cephalohematoma is typically seen at birth and

does not demonstrate erythema, warmth, or tenderness. It resolves spontaneously over 3 weeks and generally requires no treatment. Cutaneous HSV infection can mimic scalp abscess and occurs with a peak onset between 4 and 10 days of life. Prompt diagnosis and treatment of HSV is essential to prevent systemic dissemination. Aplasia cutis congenita can have clear drainage and resemble a scalp abscess.

Course, management, treatment, and prognosis

Scalp abscesses are often localized and self-limiting, leading some to suggest close monitoring with no antibiotics in the well-appearing child.⁵² However, owing to the risk of secondary complications, others have argued for the initiation of empiric antibiotics.⁵⁴ Certainly, if fluctuance develops without spontaneous suppuration, incision and drainage with subsequent Gram stain and culture to guide antibiotic management are appropriate.

NECROTIZING FASCIITIS

Necrotizing fasciitis is a potentially life-threatening infection that can arise as a complication in any number of cutaneous processes or can be without an identified incident event.⁵⁵ Ultimately, the process results in rapid progression of infection along the superficial fascial layers causing significant morbidity and mortality. Although the incidence of necrotizing fasciitis is relatively rare in neonates and infants compared with older children and adults, the outcomes can be equally devastating.

Cutaneous findings

At the site of the primary process, warmth, erythema swelling, and tenderness are typical (Fig. 12.10A). Often, the initial presentation can be difficult to distinguish from cellulitis.⁵⁶ The process can start anywhere on the body, but the abdominal wall and thorax are the most frequent initial sites of disease in neonates. Involvement of the perineum and the external genitalia is specifically referred to as Fournier's gangrene. As the infection progresses over the following 24–48 h, cutaneous findings are also likely to change. Later cutaneous signs can include a violaceous discoloration, formation of bullae initially filled with straw-colored and later bluish to hemorrhagic fluid, followed by darkening of affected tissues secondary to necrosis.⁵⁷ Despite the initial significant pain, local anesthesia can ensue denoting compromise of local nerves. Infections resulting from one organism or a combination of organisms cannot be distinguished clinically. The presence of crepitus is often noted as a sign of an anaerobic pathogen such as *Clostridium*. However, the presence of crepitus is nonspecific and can be present with other pathogens such as *E. coli*.⁵⁸

Extracutaneous findings

The clinical course of necrotizing fasciitis can vary considerably depending on the age of the patient. When considering pediatric patients of all ages, abdominal pain, vomiting, fever, chills and respiratory symptoms can be seen at presentation, while hypotension and other signs of shock are less common.^{59,60} However, rapid progression to more concerning events such as hypotension, coagulopathy and organ dysfunction is possible. For neonatal patients with necrotizing fasciitis, the initial presentation may be more ominous and include fever, tachycardia, lethargy, and poor cry.^{57,61} As the therapy for necrotizing fasciitis

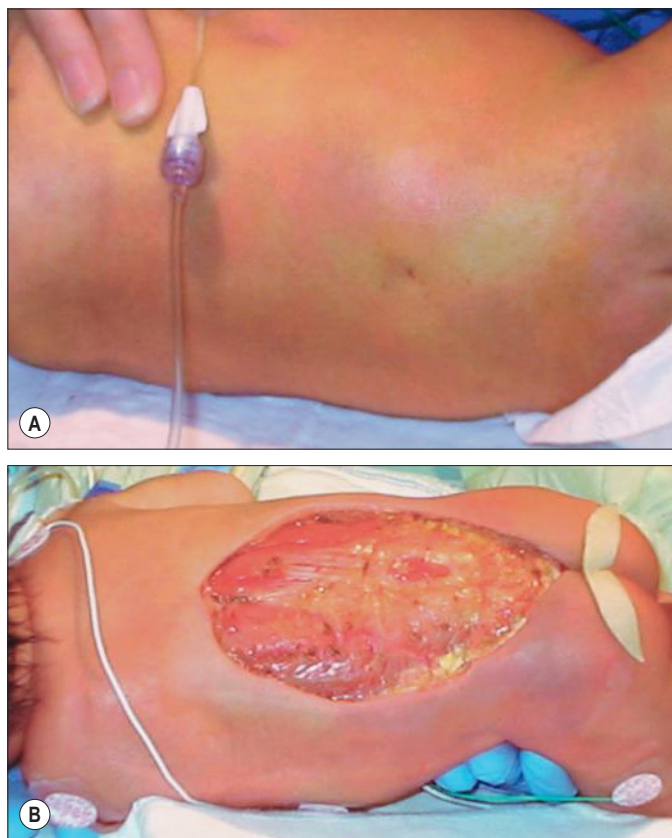


Figure 12.10 (A) Erythema and firm skin of early necrotizing fasciitis. (B) Necrotizing fasciitis: perioperative image of extent of debridement. (Courtesy of Angela Medina.)

involves surgical resection of involved tissue (Fig. 12.10B), extensive postinfectious care of large cutaneous defects is often necessary.

Etiology and pathogenesis

The microbiologic etiology of necrotizing fasciitis is often grouped as type I, which is a polymicrobial infection including at least one anaerobic pathogen and type II, which is secondary to *Strep. pyogenes* and/or *S. aureus*.⁶² Variation in the epidemiology of causative pathogens does exist across pediatric age groups.⁶³ Despite the limited number of neonatal cases, reasonable information on the microbiologic etiology and risk factors are available from multiple case reports and case series. Hsieh and colleagues reported on a review of 66 published case reports of neonatal necrotizing fasciitis.⁵⁷ Almost three-quarters of the episodes with a microbiologically documented pathogen were polymicrobial in nature. More recently, a single center study retrospectively identified 15 patients from 2002–2006 who developed necrotizing fasciitis.⁶¹ Contrary to Hsieh and coworkers, monomicrobial infection secondary to staphylococci and streptococci was more common (66%). In both reports, over 60% of the cases had a predisposing condition (i.e., omphalitis, mastitis, bullous impetigo, balanitis, necrotizing enterocolitis, or an underlying immune deficiency) or exposure (i.e., fetal scalp monitor, surgical procedure or mother with mastitis). Case reports have also implicated fungal pathogens such as zygomycetes and *Candida* spp. as the cause of necrotizing fasciitis.^{61,64}

As noted above, the initial presentation of necrotizing fasciitis may include a well-appearing child with cutaneous findings

that can include warmth, tenderness, and erythema. Often upon palpation of the involved area, the tenderness elicited is said to be out of proportion to the appearance of the skin. In the neonatal population these exam findings may be less reliable. The infection can rapidly progress to include systemic signs such as sepsis and organ failure. As the infection spreads along the fascial planes it leaves in its wake areas of necrosis.⁶⁵ Fatality rates in this patient population range from 20–59%.^{57,61}

Diagnosis

As noted above, the initial presentation of necrotizing fasciitis can be nonspecific and the cutaneous findings not convincing. Tenderness to palpation out of proportion to what would be expected based on the actual appearance of the skin should alert the physician to the possibility of necrotizing fasciitis. Assessing tenderness in a neonatal patient can be challenging and thus clinicians should be concerned if the systemic disposition of the patient is worse than might be expected based on the skin appearance. Certainly, pre-existing conditions resulting in a breach of the skin barrier, such as omphalitis, impetigo, or mastitis, should also raise suspicion for necrotizing fasciitis. A definitive diagnosis can only be made by surgical exploration and visualization of the fascia, which must be undertaken as soon as the diagnosis is suspected. Although magnetic resonance imaging (MRI), CT scan or ultrasound may aid in delineating the extent and tissue planes of involvement, these imaging studies should not delay surgical intervention. Incisional biopsy with frozen section can be useful when gross appearance of the involved tissue cannot confirm the diagnosis.⁶⁶ Histopathologically, necrotizing fasciitis shows necrosis and suppuration of the superficial fascia, edema, and an acute inflammatory infiltrate in the deep dermis, subcutaneous fat, and fascia. Tissue aerobic and anaerobic cultures should be taken at the time of the operative procedure. Additionally, blood cultures should also be drawn, as the causative pathogen is identified in the blood up to 50% of the time. Negative tissue and blood cultures do not completely exclude the possibility of necrotizing fasciitis, especially if the clinical scenario is consistent. Additional nonspecific laboratory evidence includes leukocytosis and thrombocytopenia.⁵⁷ Attempts to establish predictive rules that leverage laboratory data to accurately identify patients with necrotizing fasciitis have been published. Unfortunately, the results of these studies have been contradictory and have not been specific to neonatal patients and thus are not applicable.⁶³

Differential diagnosis

The initial cutaneous findings may be consistent with cellulitis in an otherwise stable patient. In a neonate, it is also plausible that a patient will present with systemic findings consistent with sepsis without an identified cutaneous lesion, as the lesion may not be apparent or may be covered by the diaper, clothing or blankets. It is imperative to do a full skin exam including the back, genital and perianal regions, especially if an etiology for sepsis has not been identified. Localizing the area of involvement for a patient with necrotizing fasciitis as early as possible is imperative to reducing the subsequent morbidity and mortality risk.

Course, management, treatment, and prognosis

Whenever possible, a multidisciplinary care team, including a neonatal intensive care specialist, a pediatric surgeon and a pediatric infectious disease specialist should immediately be

established. Prompt surgical intervention is mandatory. The approach of the surgeon should include an initial incision to allow direct visualization of the fascia at the involved site. If grossly necrotic tissue is realized, then proceeding to removal of all devitalized tissue down to healthy appearing and bleeding tissue is warranted. If gross visualization cannot confirm the presence or absence of necrosis, then a biopsy with subsequent pathology interpretation of the frozen section can be helpful to dictate need for further debridement.⁶⁶ Repeat exploration is generally indicated within 24–36 hours. In the interim, serial examinations should be performed and, if there is evidence of progression, then repeated surgical intervention is needed earlier. Surgery may need to be repeated on several occasions until devitalized tissue has ceased to form. Daily meticulous wound care is also paramount. Parenteral antibiotic therapy must be initiated immediately. Because monomicrobial and polymicrobial necrotizing fasciitis cannot be distinguished on clinical or surgical grounds, initial empiric therapy should include broad Gram-positive, Gram-negative, and anaerobic coverage. As with other infections, the local hospital antibiogram should help direct the need for coverage of potential resistant pathogens such as MRSA. Tissue culture data obtained at the onset of surgical intervention should inform directed antibiotic therapeutic decisions. For example if *S. pyogenes* is identified, transition to penicillin combined with clindamycin is optimal.⁶⁷ Clindamycin is added to penicillin for necrotizing fasciitis caused by *S. pyogenes* because clindamycin is more effective against *S. pyogenes* bacteria that are slowly replicating and toxin-producing.^{67,68} If a polymicrobial infection is determined by culture results, then therapy should be employed to cover each pathogen. Importantly, with a polymicrobial infection, anti-anaerobic coverage should be continued even in the absence of growth of an anaerobic pathogen, as the yield of anaerobic cultures from tissue are highly dependent on culture collection techniques.

ECTHYMA

Ecthyma refers to a red patch or nodule that necroses and ulcerates in the center due to bacterial overgrowth and disruption of blood vessels. The term ‘ecthyma gangrenosum’ is typically reserved for necrotic skin lesions specifically caused by *Pseudomonas* infection but there are other causes of ecthyma in neonates.⁶⁹

Cutaneous findings

The lesion begins as a painful red or purpuric macule, that develops a pustular or vesicular center with a surrounding rim of pink or violaceous skin that rapidly ulcerates (Fig. 12.11A). The infection also may present with bullae. The ulcer develops raised edges with a necrotic, dense, black, depressed, and crusted center. Erythema multiforme-like lesions also have been described at onset. Lesions may be single or multiple, and sometimes cluster around areas of moisture such as the mouth or perineum (Fig. 12.11B).

Extracutaneous findings

The presence of ecthyma gangrenosum in an infant is often a complication of sepsis in which the skin lesions result from bacteremic spread of infection; however, only 1.3–13% of patients septic from *P. aeruginosa* ultimately develop cutaneous lesions.⁷⁰ There have been nonsepticemic variants of ecthyma



Figure 12.11 (A) Hemorrhagic, ulcerated bulla of ecthyma gangrenosum due to *Pseudomonas aeruginosa*. (B) *Pseudomonas* septicemia with periorificial accentuation of ecthyma gangrenosum.

gangrenosum described in newborns. This localized form of ecthyma is likely from direct inoculation of the pathogen into the skin and therefore has a better prognosis.⁶⁹

Etiology and pathogenesis

Ecthyma gangrenosum is most frequently due to *P. aeruginosa*, a Gram-negative bacillus. During septicemia, the organism tends to multiply in the walls of small blood vessels, which results in arterial and venous thrombosis, and ultimately dermal necrosis.⁷¹ Risk factors in neonates and young infants include prematurity, prolonged illness, necrotizing enterocolitis, previous bowel surgery, and an immunocompromised state, especially neutropenia. There are many other organisms that have been reported to cause ecthyma that include bacterial, fungal and viral pathogens such as *S. aureus*, *Strep. pyogenes*, *Klebsiella pneumonia*, *Aeromonas hydrophila*, *E. coli*, *Proteus* spp., *Citrobacter freundii*, *Corynebacterium diphtheriae*, *Serratia marcescens*, *Stenotrophomonas maltophilia*, *Yersinia pestis*, *Aspergillus* spp., mucormycosis, and *Candida* spp.⁶⁹ The differential diagnosis for ecthyma in neonates who are premature or immunosuppressed for any reason should be appropriately broad.

Diagnosis/differential diagnosis

Lesions of ecthyma mandate a full sepsis work-up, tissue examination for Gram stain and culture, and histopathology. Gram stain is best performed on scrapings from the base of the ulceration. Histopathologic examination with proper staining for bacteria, fungi and, if indicated, virus, allows for the rapid differentiation of the source of infection. A pauci-inflammatory vasculitis, particularly of the veins, with surrounding edema, hemorrhage, and necrosis, is seen on histopathology of ecthyma gangrenosum. Bacteria may be seen in the perivascular tissue and occasionally in the vessel walls, particularly the adventitia and media of dermal veins, but not the arteries; the intima and lumina generally are spared.

Course, management, treatment, and prognosis

Ecthyma gangrenosum in association with bacteremia is a grave sign. Aggressive empiric parenteral antibiotic therapy should be initiated including a broad spectrum anti-pseudomonal agent such as cefepime, piperacillin-tazobactam, or an anti-pseudomonal carbapenem. Each of these agents also has reasonable Gram-positive coverage to include MSSA. If MRSA is suspected, vancomycin should be added. Some experts would suggest the inclusion of an aminoglycoside for broader Gram-negative coverage and additional anti-pseudomonal coverage. Finally, in an immunosuppressed, premature or critically ill child, there should be consideration for fungal coverage. Once the culture and susceptibility results are available, therapy may be narrowed.

Infections at the site of indwelling lines

When the skin is punctured and a foreign object (intravenous line or arterial line for instance) is placed, there is a risk of localized infection that can become systemic.

Cutaneous findings

Signs of catheter-related cutaneous infection include erythema, tenderness, and the presence of exudate at the exit site. Infection can occur at the catheter exit site, along the tunnel, or at its site of insertion into the vessel.⁷²

Extracutaneous findings

Children can become bacteremic and possibly septic from the infected catheter site and can seed other organs with bacteria. Signs of systemic spread would include fever, lethargy, and temperature instability. *S. aureus* tends to lead to more fulminant infection. Coagulase-negative *Staphylococci* can cause indolent disease, although they are capable of producing fulminant infections. In developed countries, coagulase-negative staphylococci are the principal agents of sepsis in premature neonates.^{72,73} They also are an important cause of septicemia in neonates in many developing countries. Additional extracutaneous infections caused by coagulase-negative staphylococci include infective endocarditis, CSF shunt infections, necrotizing enterocolitis, pneumonia, urinary tract infection, and osteomyelitis.

Etiology and pathogenesis

Infection occurs because of the disruption of host defense mechanisms resulting from placement of the indwelling medical device. Any bacteria that colonize the skin can be pathogenic in

this setting, especially in preterm or immunosuppressed infants. The normal human flora includes 13 species of coagulase-negative staphylococci. These colonize the skin of most neonates within 2–4 days of birth,⁷⁴ are of relatively low virulence, and typically do not cause infection. However, they are an important cause of sepsis in preterm infants and may cause cutaneous infection. *Staphylococcus epidermidis* is the most prevalent member of this group, making up 60–90% of the coagulase-negative *Staphylococci* on the skin. The most important causes of clinical disease are *S. epidermidis* and *S. haemolyticus*. Colonization of the skin is a prerequisite for infection, and development of disease generally requires compromise of the epidermal barrier. Heavy skin colonization is a risk factor for the development of catheter-related infection. The increased incidence of infection in preterm infants is likely multifactorial but in part, may be due to the defective neutrophil oxidative burst compared with term infants.⁷⁵

Diagnosis

Gram stain and cultures of skin and a culture of the blood via the line are important. Because this organism colonizes the skin, clinical correlation is necessary to determine whether it is the cause of the clinical disease. The line should be removed as early as possible.

Course, management, treatment, and prognosis

Strict handwashing is essential to limit the spread of such pathogens within the neonatal nursery. Recently, cleansing with chlorhexidine prior to line placement has been recommended in infants over 2 months of age to prevent line infections.⁷⁶ When infection at the site of an indwelling catheter is suspected, broad Gram-positive coverage with an agent such as vancomycin should be initiated. In a child with signs of systemic infection, the addition of Gram-negative coverage is warranted. The treatment regimen can be modified appropriately once antibiotic susceptibility results are available.

Purpura fulminans

Purpura fulminans (PF) is a potentially disabling and life-threatening disorder characterized by an acute onset of progressive cutaneous hemorrhage and necrosis caused by dermal vascular thrombosis, and disseminated intravascular coagulation (DIC).⁷⁷ Purpura fulminans usually arises in previously healthy neonates who become systemically ill, especially from meningococcal sepsis, varicella, pneumococcal sepsis, and meningitis.⁷⁸

Cutaneous findings

Cutaneous erythema with or without edema and petechiae develops first. Sites of involvement appear transiently to resemble ecchymoses, and up to this point, the pathologic process in the skin is reversible without progression to necrosis. Lesions evolve rapidly into painful, indurated, well-demarcated, irregularly bordered purpuric papules and plaques surrounded by a thin, advancing erythematous border. Late findings in necrotic areas are the formation of vesicles and bullae, which mark the development of hemorrhagic necrosis (Fig. 12.12), and finally firm eschar, which ultimately sloughs. The distal extremities are often the most severely involved, usually in a symmetric manner. This is probably a result of fewer collateral channels for tissue perfusion, and the relatively greater impact of circulatory



Figure 12.12 Purpuric plaques with bullae formation in purpura fulminans due to *N. meningitidis*.

collapse on perfusion of distal vascular beds. Acute infectious PF tends to progress proximally to form purpuric plaques of various sizes and shapes in a patchy distribution.

Extracutaneous findings

Shock is characteristic of acute infectious PF, and the development of systemic consumptive coagulopathy (i.e. DIC) is a defining feature. Thrombohemorrhagic manifestations may be found in multiple vascular beds and organ systems, and multiple organ dysfunction syndromes are common. Massive non-traumatic subdural hematoma can occur in extremely premature infants. Fibrinogen, coagulation factors (e.g., factors V and VIII), and platelets are consumed in ongoing thrombosis and fibrinolysis. Prothrombin time (PT) and partial thromboplastin time (PTT) are prolonged; fibrin degradation products (e.g., D-dimers) are elevated; and protein C, protein S, and antithrombin III levels are reduced.

Etiology/pathogenesis

Purpura fulminans develops in 15–25% of individuals with meningococcemia.⁷⁹ In the neonate, acute infectious PF may be caused by early- or late-onset group B *Streptococcus* (GBS) disease, or occasionally a number of other Gram-positive and Gram-negative pathogens. PF results from an imbalance between anticoagulant and procoagulant activities of endothelial cells, shifting to a state of increased coagulation. In PF caused by *Neisseria meningitidis* this shift to a procoagulant state is triggered by endotoxin, producing an increase in interleukin (IL)-2, interferon- γ , tumor necrosis factor (TNF)- β , and IL-1, and leading to consumption of proteins C and S and antithrombin III.⁷⁷

Diagnosis

Neisseria meningitidis can sometimes be identified as the cause of PF initially by finding the Gram-negative diplococci on Gram stain of material obtained by needle aspiration of a petechial skin lesion,⁸⁰ or by scraping the lesion with a needle and making a smear of blood.⁸¹ The histopathologic hallmarks of PF are dermal vascular thrombosis and secondary hemorrhagic necrosis.⁸² Vasculitis, including a perivascular neutrophilic infiltrate, is a characteristic feature.

Differential diagnosis

Purpura fulminans in the neonatal period may be a manifestation of inherited, homozygous protein C, or rarely, protein S deficiency.⁸³ Congenitally acquired infection with rubella, toxoplasmosis, and cytomegalovirus, and postnatally acquired infection with herpes simplex virus, viral hepatitis, certain enteroviruses, and respiratory syncytial virus, can produce purpura. Non-infectious causes of purpura in neonates include birth trauma, blood group incompatibility, neonatal isoimmune thrombocytopenia, maternal idiopathic thrombocytopenia purpura, maternal lupus erythematosus, drugs administered to the mother, Kasabach–Merritt syndrome, thrombocytopenia absent radius (TAR) syndrome, congenital histiocytosis, disseminated intravascular coagulation (DIC), congenital leukemia, and child abuse.⁸⁴

Course, management, treatment, and prognosis

The size of the skin hemorrhage increases with disease severity, and the presence of purpura, particularly when generalized, is associated with high morbidity and mortality.⁸⁵ Many who survive PF have cutaneous and/or skeletal deformities resulting from gangrene. Initial management of the patient with acute infectious PF must be focused on preserving life through respiratory and hemodynamic support and prompt broad-spectrum intravenous antibiotic coverage. Initial empiric therapy with a third-generation cephalosporin such as cefotaxime or ceftriaxone, is reasonable when targeting *N. meningitidis*.⁸⁶ In immunocompromised patients, such as those with neutropenia, expanding coverage to include anti-pseudomonal activity is necessary. Additionally, if *S. aureus* is suspected and local rates of MRSA are increased, then the initiation of vancomycin may be necessary. Antibiotic therapy can be adjusted after the organism has been recovered and its susceptibility profile determined. Surgical consultation should be sought early in the course to monitor compartment pressures and intervene in compartment syndrome. Nutritional support is also important and should be continued during the rehabilitative phase. Therapeutic interventions that should be initiated for all patients with PF and DIC include vitamin K and fresh frozen plasma (FFP, 8–12 mg/kg every 12 hours) to correct possible deficiencies of vitamin K-dependent coagulation factors, antithrombin III, protein C, and protein S. A number of other newer, non-conventional treatment modalities, including concentrates of protein C or antithrombin III, recombinant tissue-type plasminogen activator, prostacyclin, plasmapheresis, hyperbaric oxygen, and a host of targeted immunotherapies (e.g., IL-1 receptor antagonist, monoclonal antibody to TNF- β , anti-endotoxin antibodies, platelet-activating factor receptor antagonist, and pentoxifylline) are available in some centers but the effectiveness of each of these interventions is unproven.⁷⁷

Close contacts of patients with invasive meningococcal disease should receive prophylaxis with rifampin (or possibly ciprofloxacin for those aged 18 or over) as soon as possible. Options for prophylaxis include rifampin every 12 hours for 2 days or one dose of ceftriaxone intramuscularly. Patients at risk for meningococcal disease, such as those with complement or properdin deficiency, should be vaccinated. Current recommendations suggest that children down to age 9 months with a condition that predisposes them to meningococcal disease receive two doses of the quadrivalent meningococcal conjugate vaccine (MCV-4). Depending on the patient's age, the second

dose should be given either 2 (for age 2–18 years) or 3 (for age 9–23 months) months apart.⁸⁷

Toxin-mediated disease

Exotoxin-mediated diseases are caused by the effects of extracellular toxins produced at a focus of infection or colonization. The site of bacterial replication is typically inconspicuous in relation to the clinical effects of the toxins. Toxins can act locally, as in bullous impetigo, or can cause widespread clinical signs resulting from hematogenous spread, as seen in staphylococcal scalded skin syndrome.

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Staphylococcal scalded skin syndrome (SSSS) is a staphylococcal epidermolytic toxin-mediated disease characterized by cutaneous tenderness and superficial, widespread blistering and/or desquamation.⁸⁸ In the neonatal period, nursery outbreaks of the disease are described.⁸⁹

Cutaneous findings

Exquisite tenderness of the skin may herald the onset of SSSS. Generalized macular erythema evolves rapidly into a scarlatini-form eruption that is accentuated in flexural and periorificial areas (Fig. 12.13). The brightly erythematous skin acquires a wrinkled appearance, leading to thick flaky desquamation, particularly in the flexures, over approximately 2–5 days. In severe cases, the erythrodermic phase is followed by the development of diffuse, sterile, flaccid blisters and erosions, and diffuse, bullous desquamation of large sheets of skin (Fig. 12.14). At this stage, areas of epidermis may separate in response to a gentle shear force (Nikolsky's sign). As large sheets of epidermis peel away, moist, glistening, denuded areas become apparent, initially in the flexures and subsequently over much of the body surface. As the exposed denuded skin dries, it develops a crusted, flaky appearance. Distinctive radial crusting and fissuring around the eyes, mouth, and nose develop approximately 2–5 days after the onset of erythroderma. Secondary cutaneous infection, cellulitis, omphalitis, and severe surgical wound infections may occur.

Extracutaneous findings

Complications may include excessive fluid loss, electrolyte imbalance, faulty temperature regulation, pneumonia, endocarditis, and septicemia. Mortality, due predominantly to sepsis, is unusual, but is highest in the severe generalized form of the disease.

Etiology and pathogenesis

SSSS is caused predominantly by phage group II staphylococci, particularly strains 71 and 55; occasionally, a group I or III isolate is involved.⁹⁰ Foci of infection include the nasopharynx, or less commonly the umbilicus, urinary tract, a cutaneous wound, conjunctivae, blood, and rarely through breastfeeding.⁹¹ These bacteria produce epidermolytic (i.e. exfoliative or exfoliating) toxins A (ETA), B (ETB), and/or D.^{92,93} ETB is more frequently associated with generalized SSSS than ETA. A reduced concentration of antibodies directed against ETB and an increased ability to penetrate into the bloodstream may explain why ETB is associated more frequently with SSSS.¹⁰ These epidermolytic toxins induce bulla formation by cleaving

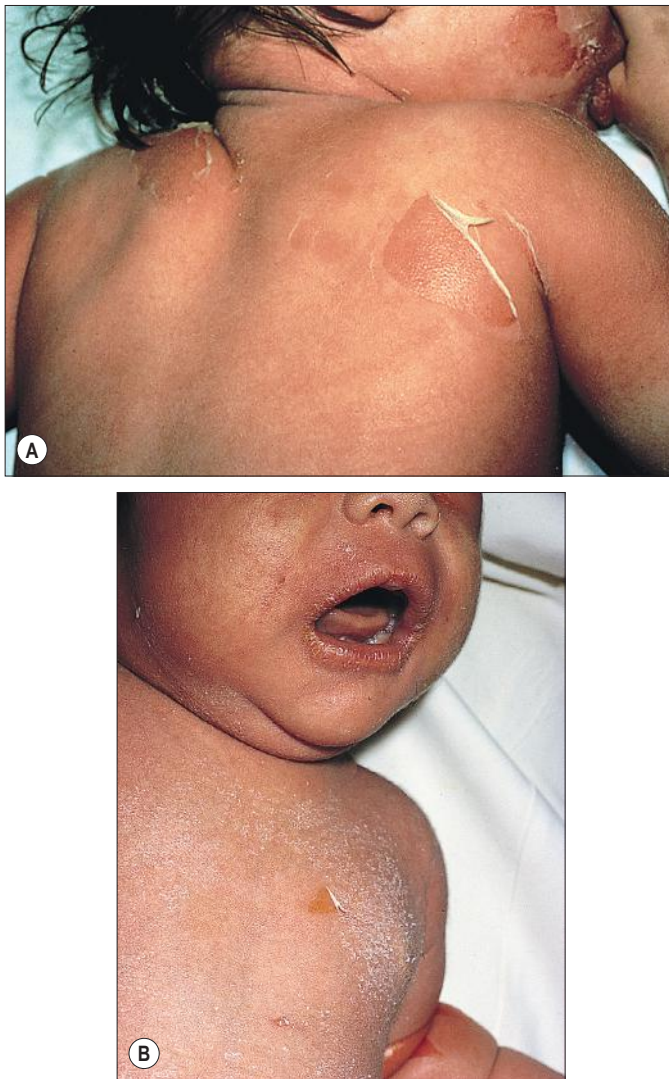


Figure 12.13 (A) Diffuse erythroderma and Nikolsky's sign in staphylococcal scalded skin syndrome. (B) Staphylococcal scalded skin syndrome: note the perioral accentuation which is characteristic. (A: From Darmstadt GL. *Staphylococcal and streptococcal skin infections*. In: Harahap M, ed. *Diagnosis and treatment of skin infections*. Oxford: Blackwell Science; 1997. Courtesy of Alfred T. Lane.)



Figure 12.14 Widespread SSSS with erosions and scaly areas of desquamation.

desmoglein I within desmosomes, via serine proteases. The severity of the disease is related to the toxin load, rather than the nature of the focal infection, and this load may be particularly high in neonates owing to reduced renal clearance.⁹⁰

Diagnosis

Recovery of a toxin-producing strain of *S. aureus* in a neonate or infant with widespread blistering establishes the diagnosis of SSSS. Although intact bullae on the skin are sterile, cultures should be obtained from multiple sites, including the blood, cerebrospinal fluid, nasopharynx, urine, umbilicus, and any suspected sites of localized infection, in an attempt to identify the source of the epidermolytic toxins. Histopathologically, subcorneal bulla formation through the granular layer without an inflammatory infiltrate is characteristic (Fig. 12.15). In cases that demand a rapid diagnosis, the exfoliated corneal layer can be seen on a frozen biopsy specimen of the desquamating epidermis. Scattered acantholytic cells that are evident histopathologically in the cleft-like bullae can also be seen in a Tzanck preparation.

Differential diagnosis

SSSS may be mistaken for a number of other blistering and exfoliating disorders, including scarlet fever, bullous impetigo, Kawasaki disease, epidermolysis bullosa, diffuse cutaneous mastocytosis, familial peeling skin syndrome with eosinophilia, epidermolytic hyperkeratosis, a viral exanthem, a drug eruption, erythema multiforme, and Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). SJS and TEN often can be distinguished by a history of drug ingestion, the presence of Nikolsky's sign only at sites of erythema, and presence of mucosal blistering. The differentiation of SJS/TEN from SSSS may occasionally require a skin biopsy. SJS/TEN result in full-thickness epidermal necrosis, with a blister cleavage plane in the lowermost epidermis. Distinguishing between these conditions is particularly important because overall mortality rates as high as 30% have been reported with TEN, and avoidance of the offending drug is crucial to prevent recurrence.

Course, management, treatment, and prognosis

Recovery is usually rapid once appropriate antibiotic therapy has begun. Parenteral nafcillin or oxacillin should be given promptly. In regions where MRSA is prevalent, vancomycin should be considered. Strict isolation is imperative to avoid the spread of infection. (See Chapters 10 and 11 for skin care recommendations in blistering diseases.) General principles include minimizing the handling of the infant, and the use of emollients (e.g., petrolatum and petroleum jelly gauze) and semi-occlusive dressings to provide lubrication and minimize pain. Corticosteroids are detrimental and should be avoided. Healing occurs without scarring in 10–14 days.

TOXIC SHOCK SYNDROME

Toxic shock syndrome (TSS) is a severe acute infection characterized by fever, widespread macular erythema, shock, and multisystem organ failure. Toxins produced by certain strains of *Strep. pyogenes* and *S. aureus* act as superantigens leading to hypotension due to extreme activation of the immune system with cytokine release.

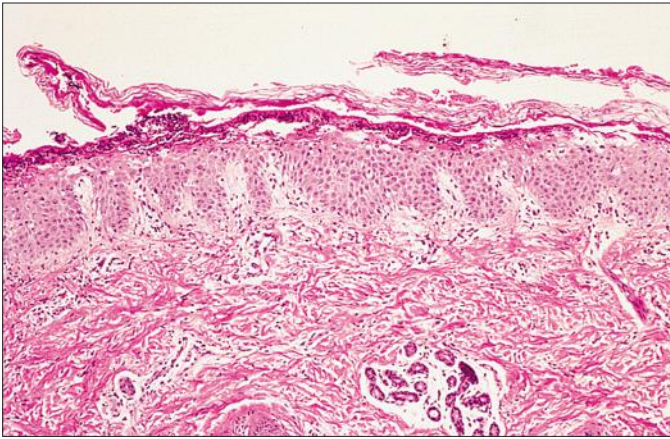


Figure 12.15 Skin biopsy of SSSS reveals a subcorneal split at the level of the stratum granulosum.

Etiology and pathogenesis

TSS is caused by a primary infection with either *S. aureus* or *Strep. pyogenes* that produce toxins that directly activate the immune system bypassing the usual antigen-mediated immune response system.⁹⁴ Staphylococcal TSS occurs most frequently after primary cutaneous infection or infection secondary to surgery, foreign body or burns infections but sometimes the primary infection is not apparent.^{95,96} Staphylococcal TSS is caused primarily by an overproduction of toxic shock syndrome toxin 1 (TSST-1), but enterotoxins A, B and C have also been implicated.⁹⁷ Streptococcal TSS can develop in various clinical settings including, but not limited to: cellulitis, pneumonia, septic arthritis, or pharyngitis.⁹⁸ Most isolates of *Strep. pyogenes* that cause STSS are M protein types 1, 3, 12, and 28 that produce streptococcal pyrogenic exotoxins A and/or B.^{94,99,100} Lack of antibody against exotoxin appears to be a risk factor for severe, invasive disease and streptococcal TSS.⁹⁴

Cutaneous findings

Staphylococcal TSS manifests as widespread erythema with accentuation in the skin folds. There is commonly a strawberry tongue and there is characteristic peeling of the hands, feet and sometimes perineum within 1–2 weeks.⁹⁷

The primary *Strep. pyogenes* infection for some patients will include cellulitis, fasciitis, or myositis. In patients with these manifestations, development of severe pain at the site of infection is common. Primary varicella zoster virus infection (chickenpox) is also a risk factor for streptococcal TSS.⁹⁴ Additionally, cutaneous findings are not always seen but can include erythroderma. The development of vesicles and bullae (5%) is a late, ominous sign of tissue devitalization.^{101,102} Other cutaneous signs in a minority of patients include a petechial, maculopapular, or diffuse scarlatiniform eruption.

Extracutaneous findings

In streptococcal TSS, patients without a soft tissue infection may have a variety of other focal infections that serve as the source of *S. pyogenes*, including endophthalmitis, osteomyelitis, myositis, pneumonia, perihepatitis, peritonitis, myocarditis, and sepsis.¹⁰² TSS can be acute or insidious in onset but most commonly presents with fever, generally accompanied by tachycardia and hypotension. There is then progression to shock and multiorgan compromise or failure that may include the kidneys, liver, hematologic systems and/or central nervous systems as noted below. Criteria for diagnosis of TSS are summarized in

Box 12.2.^{103,104}

Course, management, treatment, and prognosis

Patients suspected of having TSS should be managed in an intensive care setting because of the rapidly progressive, fulminant nature of the syndrome. Management consists of aggressive intravenous fluid resuscitation, culture of potential sites of infection, early surgical exploration of suspected deep-seated infections with debridement of devitalized tissue, removal of any potential foreign body nidus of infection and prompt administration of antibiotics. Inotropic agents may be necessary to manage shock due to toxic cardiomyopathy. The use of epinephrine (adrenaline) in patients with intractable hypotension may potentiate gangrene of digits. The use of intravenous immunoglobulin is still controversial but sometimes recommended in the setting of refractory disease. While ruling out

septic shock from Gram-negative bacilli or polymicrobial necrotizing fasciitis, broad-spectrum antimicrobial therapy should be initiated. If a diagnosis of streptococcal TSS is made, therapy can be tailored to include an agent active against the cell wall of *S. pyogenes* such as penicillin. The addition of clindamycin has been recommended as an adjunctive therapy with the advantage of decreasing bacterial toxin production.¹⁰⁵

Other infectious agents

There are a few bacterial pathogens that are either more specific to, or show unique cutaneous presentations in, neonates and infants and thus will be discussed separately.

GROUP B STREPTOCOCCUS

Group B *Streptococcus*, GBS, or *Streptococcus agalactiae*, a Gram-positive bacteria, is one of the most common causes of neonatal septicemia in developed countries. There are early and late forms of GBS disease. Early-onset disease presents within the first 6 days of life, although signs of infection are typically present at birth or within hours of delivery; preterm infants are particularly susceptible. Late-onset disease occurs from 7 days to 3 months of life, with a median age at onset of 27 days. The terminology of late, late onset is reserved for those infections presenting after 3 months of life.

Cutaneous findings

Cutaneous manifestations of GBS infection are rare.¹⁰⁶ Skin lesions, however, may be an early sign of bacteremia or, alternatively, may provide a focus of infection from which bacteremia may occur. Cellulitis is the most common cutaneous manifestation of GBS infection and typically develops in late-onset disease. GBS cellulitis has a predilection for the face, submental, and submandibular regions in infants less than 12 weeks of age. Additional GBS soft tissue presentations have included facial or submandibular cellulitis with ipsilateral otitis media,¹⁰⁷ and inguinal (Fig. 12.16), scrotal, prepatellar, or retropharyngeal. This organism can cause vesicles, bullae, and erosions that resemble impetigo.¹⁰⁸ The lesions may be present at birth and appear anywhere on the body. Additional cutaneous manifestations of GBS infection include abscesses of the scalp, breast, submandibular gland, and subcutaneous tissue; erythema nodosum-like lesions; conjunctivitis; necrotizing fasciitis; acute necrotizing cellulitis of the scrotum; and purpura fulminans.

Extracutaneous findings

Extracutaneous findings vary depending on the timing of disease onset. Early-onset disease is characterized by septicemia, respiratory distress, apnea, shock, pneumonia, and less commonly, meningitis (5–15%). Bacteremia without a focus of infection (40–50%) is the most common presentation of late-onset disease, although other foci such as osteomyelitis, septic arthritis, and cellulitis/adenitis may be found. Cellulitis usually is associated with bacteremia (90%).

Etiology and pathogenesis

Cutaneous manifestations of GBS infection may be due to primary infection of the skin, often in association with surgery (e.g., circumcision) or cutaneous trauma (e.g., fetal scalp monitoring), or as a result of tertiary infection of the skin during

BOX 12.2 DIAGNOSIS OF TOXIC SHOCK SYNDROME

In order to meet the criteria to define staphylococcal TSS,¹⁰³ there needs to be negative blood, throat and cerebrospinal fluid cultures (except if *S. aureus* grows) and negative tests for rocky mountain spotted fever, measles and leptospirosis in addition to four (probable) or five (confirmed) criteria:

- Fever $\geq 38.9^{\circ}\text{C}$.
- Diffuse erythroderma
- Desquamation 1–2 weeks after onset of illness
- Hypotension
- Multisystem involvement (three or more):
 - Gastrointestinal: vomiting or diarrhea
 - Muscular: myalgia or elevated CPK
 - Mucous membrane: vaginal, oropharyngeal or conjunctival hyperemia
 - Renal: blood urea nitrogen or creatinine at twice normal values in the absence of urinary tract infection
 - Hepatic: total bilirubin, alanine aminotransferase or aspartate aminotransferase over twice normal values
 - Hematologic (platelets over $100 \times 10^9/\text{L}$)
 - Central nervous system: disorientation or alterations in consciousness

A proven diagnosis of streptococcal TSS¹⁰⁴ requires isolation of *S. pyogenes* from a normally sterile site in a patient with hypotension and two or more additional findings:

- Renal impairment
- Coagulopathy: platelets $<100 \times 10^9/\text{L}$, or disseminated intravascular coagulopathy
- Hepatic impairment: total bilirubin, alanine aminotransferase or aspartate amino transferase over twice normal values
- Respiratory distress syndrome
- A generalized erythematous rash, with or without desquamation
- Soft tissue necrosis (myositis, fasciitis)

Courtesy of Division of Health Informatics and Surveillance <http://wwwn.cdc.gov/NNDSS/script/casedef.aspx?CondYrID=868&DatePub=1/1/1997%2012:00:00%20AM>



Figure 12.16 Red nodules of Group B streptococcal cellulitis. (Courtesy of Kiran Patel, MD and Nicole Hames, MD.)

bacteremia. Colonization of the neonate as a prelude to infection is thought to occur either in utero, via the ascent of organisms, or during delivery. Approximately 30% of women are carriers of GBS, yet only 1–2% of their infants develop early-onset disease, indicating that neonatal infection reflects a complex interaction between host defenses and bacterial virulence factors. In general, the likelihood of neonatal infection increases with greater bacterial inoculum, duration of exposure, and immaturity of the host. Infants who develop either early- or late-onset disease have low levels of antibody to type III polysaccharide, one of the organism's major virulence factors.¹⁰⁹

Diagnosis

The organisms may be visualized on Gram stain and recovered in cultures from skin lesions. Because skin findings may be an early indicator of occult bacteremia, evaluation should include urine, blood, and CSF cultures and a chest radiograph.

Differential diagnosis

Other bacterial organisms producing non-necrotizing soft tissue infections (e.g., impetigo, cellulitis, abscess), necrotizing soft tissue infections (e.g., necrotizing fasciitis) or purpura fulminans in the neonate can mimic GBS infection.

Course, management, treatment, and prognosis

Parenteral penicillin remains the drug of choice, but initial therapy for suspected GBS infection should consist of ampicillin and an aminoglycoside such as gentamicin, because this regimen provides broad coverage for the important pathogens in neonatal septicemia as well as synergic action against GBS. Once GBS has been identified as the pathogen and the bloodstream and CSF have been shown to be sterile for 24–48 hours, penicillin G alone can be given.¹¹⁰ The duration of therapy required for treatment of GBS skin infections depends on the nature and severity of the infection and the involvement of other sites (e.g., bloodstream, meninges). Interestingly, in a small case series of five patients with GBS cellulitis, all five had

received ampicillin and gentamicin for at least 3 days for other indications prior to the onset of cellulitis. This suggests that neonatal GBS colonization persists, despite systemic antibiotic exposure.¹¹¹ When there is GBS-induced meningitis, 30–50% of the neonates will have permanent neurologic defects.¹¹² Overall mortality rates have improved greatly, from 50% in the 1970s to 5–6% in recent years.¹¹³ Vaccination against GBS is a potential effective method of prevention, but candidate vaccines are still under development.¹¹⁴

LISTERIA MONOCYTOGENES

Listeria monocytogenes is an uncommon cause of infection in newborn infants, with an incidence of 5.2 cases/100 000 live births. More recent data from Northern California suggest that the incidence of neonatal bacteremia secondary to *Listeria monocytogenes* is negligible.¹¹⁵ Worldwide, however, it is one of the three major causes of neonatal meningitis.¹¹⁶ Similar to infection with group B *Streptococcus*, affected infants present with disease shortly after birth, or with a late-onset form that generally develops between 2 and 5 weeks of life. Skin lesions, however, have only been described in early-onset disease.

Cutaneous findings

Lesions are usually evident at birth. Generalized petechiae and erythematous macules progress to erythematous pustules.¹¹⁷ Purulent conjunctivitis may also occur. Focal infection may occur from direct skin inoculation. Granulomatosis infantum septicum are widely disseminated granulomatous abscesses that are characteristic of severe listeriosis.¹¹⁶ These lesions are not only on the skin but can be seen in the liver, placenta, brain, spleen, kidneys, lungs, and GI tract.

Extracutaneous findings

Neonates with early-onset disease generally are delivered prematurely to mothers with a febrile illness and are septicemic (80%). Other symptoms include acute respiratory distress, pneumonia, meningitis, and myocarditis. Late-onset disease is usually seen days to weeks after an uncomplicated full-term delivery, with signs of sepsis or meningitis, including irritability, fever, lethargy, and diarrhea.

Etiology and pathogenesis

Listeria monocytogenes is usually acquired by the pregnant female via the consumption or aspiration of contaminated meat, raw dairy products, or raw vegetables.¹¹⁶ Affected pregnant women develop an influenza-like illness that may include vertical transmission to the fetus via hematogenous spread to the placenta, from an ascending vaginal infection, or during passage through the birth canal.¹¹⁸ Rarely, infection may result from cross-contamination in the delivery suite or nursery. The highest concentrations of organisms are found in the lungs and gut of the neonate, suggesting that infection may be acquired in utero via infected amniotic fluid. The organism has a predilection for the placenta and, once invasive disease has occurred, the central nervous system.

Diagnosis

A full sepsis evaluation should be performed in infants with suspected listeriosis, including bacterial cultures of the blood, urine, and CSF. The diagnosis may be aided by obtaining Gram stains and cultures from the mother's vagina, the amniotic fluid,

and the infant's meconium, gastric washings, skin, posterior pharynx, and conjunctivae. Gram staining of meconium may be particularly revealing in granulomatosis infantisepticum. Cutaneous pustules show Gram-positive rods, but the organism may appear as cocci in pairs and simulate pneumococcus. *L. monocytogenes* also can produce white plaques on the surface of the cord. Serologic tests are not useful because of lack of sensitivity.

Differential diagnosis

Other pathogens that can cause a generalized vesiculopustular eruption must be excluded (see Chapter 10). The other pathogen that characteristically shows involvement of the umbilical cord is *Candida*.

Course, management, treatment, and prognosis

Infection acquired in utero may result in death of the fetus or congenital listeriosis. Early-onset *Listeria* infection in the first 2 days of life carries a 30% mortality rate, although mortality rates up to 38–60% have been reported.^{119,120} *L. monocytogenes* is sensitive in vitro to many antibiotics, including penicillin, ampicillin, erythromycin, trimethoprim-sulfamethoxazole, chloramphenicol, rifampin, tetracyclines, and aminoglycosides, but it is always resistant to cephalosporins.¹²⁰ Although there have not been any controlled trials to determine optimal first line therapy, most experts recommend parenteral ampicillin and an aminoglycoside, such as gentamicin, which provides synergy against *L. monocytogenes*. After an adequate clinical response has been achieved, a course of therapy (10–14 days for invasive disease without meningitis, 2–3 weeks if meningitis is present) can be completed with ampicillin or penicillin alone.¹¹⁶

TREPONEMA PALLIDUM

Congenital syphilis (CS) occurs in infants born to mothers infected with the spirochete *T. pallidum*. In the 1980s and 1990s, the number of reported cases of CS and maternal syphilis in the USA increased, subsequently decreased to its lowest point in 2004 but unfortunately increased again nationwide from 2005–2008.¹²¹ Between 28% and 35% of neonates with CS had mothers who did not receive prenatal care.¹²² The lack of historical and laboratory data to make a diagnosis of CS in these cases emphasizes the importance of recognizing the dermatologic features of the disease.

Congenital syphilis is divided into early and late disease. Early disease usually presents before 3 months of age, although signs can appear anytime in the first 2 years of life. Late disease appears after age 2 years.

Cutaneous findings

Overall, approximately half of newborns with CS are asymptomatic at birth. Cutaneous findings, although highly variable, are present in only 38% of those affected.¹²³ The palmar/plantar, perioral, and anogenital regions are classically involved. Mucous membrane involvement may present as snuffles (syphilitic rhinitis), which is often the first sign of CS. Syphilitic rhinitis begins as clear nasal discharge that may be mistaken clinically for a viral upper respiratory infection and may become profuse, chronic, and/or bloody. Associated inflammation and ulceration of the nasal mucosa can result in perforation of the nasal septum, with subsequent alteration of the nasal cartilage (saddle nose deformity). Condyloma lata refers to the highly infectious

flat-topped papules and plaques that occur at the mucocutaneous junctions of the nares, angles of the mouth, and in the anogenital region; chronic induration in these areas leads to rhagades, or linear scars, which fan out from the corners of the mouth and the affected orifices. Mucous patches may also occur on the lips, tongue, and palate. Other early findings include petechiae (usually from thrombocytopenia), hemorrhagic vesicles and bullae (pemphigus syphiliticus), and erythematous macular, papulosquamous, annular, or polymorphous eruptions (Fig. 12.17). The papulosquamous eruption is most common on the posterior aspects, particularly the buttocks, back, and thighs, in addition to the soles. Although the papulosquamous rash resembles the coppery-red eruption of acquired secondary syphilis, pemphigus syphiliticus is unique to the newborn. Bullae form on an indurated, red base and rupture easily, leaving a macerated area that may form crusts. Changes on the palms and soles include erythema with a polished appearance; superficial peeling; indurated fissures; and oval ham-colored macules and papules that acquire a coppery-brown color as they age. Nail deformities, paronychia, and alopecia may occur. Untreated skin lesions resolve in 1–3 months with postinflammatory hyperpigmentation and/or hypopigmentation, but dyspigmentation is infrequent in the newborn period.



Figure 12.17 Papulosquamous plaques in two infants with syphilis.

Extracutaneous findings

CS commonly presents with extracutaneous findings that include low birthweight, hepatomegaly with elevation of serum alkaline phosphatase, splenomegaly, anemia, thrombocytopenia, jaundice, osteochondritis, generalized lymphadenopathy, respiratory distress, hydrops fetalis, meningitis, meningoencephalitis, nephrotic syndrome, chorioretinitis, and pseudoparalysis.¹²³ Late manifestations (i.e., appearing after 2 years of age) involve the central nervous system (neurosyphilis, which may be asymptomatic), bones (frontal bossing, saddle nose, concave central face, saber shins, Clutton's joints), teeth (Hutchinson peg-shaped notched central incisors, mulberry multicuspid first molars), skin (rhagades, nodular syphilids, gummata), eyes (interstitial keratitis, optic atrophy), and ears (eighth-nerve deafness). Hutchinson's triad of defects includes interstitial keratitis, defects of the incisors, and sensorineural hearing loss.

Etiology and pathogenesis

Infection occurs via invasion of the placenta by the spirochete *T. pallidum*. The organism enters the bloodstream directly and invades the liver, with subsequent invasion of other organs, principally the skin, mucous membranes, bones, and central nervous system. Infection can occur at any time during pregnancy or at birth. Spirochetes preferentially adhere to endothelial cells and induce vasculitis. Nearly all neonates born to mothers with primary or secondary syphilis sustain congenital infection, but only about 50% are clinically symptomatic at birth.¹²⁴ A high percentage will be preterm and at high risk for neurologic complications. As many as 25–40% of infected fetuses of mothers with untreated syphilis die in utero.¹²⁵ Neonates infected during the third trimester typically are normal at birth, may become ill during the first weeks of life, but most commonly show signs at 2–6 weeks of age.

Diagnosis

The laboratory diagnosis of CS may be difficult because false-positive and -negative serologies confound interpretation and because *T. pallidum* cannot be cultured on artificial media.¹²⁶ Maternal nontreponemal and treponemal IgG antibodies can be present in the fetus as a result of transplacental transfer even if the mother was adequately treated during pregnancy. Serum should be taken from the infant, rather than from cord blood, as the latter has yielded false-negative results especially when the mother was infected late in pregnancy.¹²⁷ The diagnosis can be made by demonstration of spirochetes within a clinical specimen, obtained by scraping the base of a mucocutaneous lesion, using darkfield microscopy or direct fluorescent antibody testing. Specimens from mouth lesions require direct fluorescent antibody techniques to distinguish *T. pallidum* from commensal oral spirochetes. Histopathologic examination of the placenta and umbilical cord using specific fluorescent anti-treponemal antibody staining also is recommended. Knowledge of the syphilis status for all new mothers should be documented in their newborn's chart prior to discharge. A syphilis diagnosis should be strongly considered for a newborn if the mother had clinically documented syphilis during pregnancy or had reactive nontreponemal and treponemal tests before or during pregnancy. Additional intervention for the child depends on confirmation of appropriate treatment for the mother either before or during pregnancy. If treatment was before pregnancy

and the child is well, no further intervention is required. If the mother's treatment was not appropriate during pregnancy, then treatment of the child is necessary. If intrapartum treatment for the mother was appropriate then the decision to treat the child is based on the child's serum nontreponemal titer (VDRL, RPR) results. If the infant's nontreponemal test is four-fold the mother's level, then the diagnosis of congenital syphilis is made and treatment administered; a titer less than four-fold that of the mother, however, does not exclude CS.¹²⁸ Nontreponemal tests in both an infected mother and her congenitally infected infant may be falsely negative if the mother acquired the disease late in pregnancy, or in the case of a prozone phenomenon. False-positive reactivity of nontreponemal tests can be caused by certain infectious diseases (e.g., hepatitis, varicella, measles, infectious mononucleosis, tuberculosis, malaria, endocarditis), malignancies (e.g., lymphoma), and connective tissue disease (e.g., systemic lupus erythematosus). The nontreponemal tests are useful for screening, and, if reactive, should always be confirmed using a treponemal test. A CSF VDRL test should be performed on all neonates when there is a suspicion for CS, remembering that a negative result does not exclude neurosyphilis. A false-positive result, however, may occur in an uninfected newborn with a transplacentally acquired high serum VDRL titer. Newer techniques may improve our diagnostic capabilities, including immunoblotting to detect IgM against a 47 kDa membrane protein and PCR amplification of the genomic region encoding this same membrane protein.¹²⁹ A skin biopsy is helpful in the evaluation of CS and shows swelling and proliferation of endothelial cells, and a predominantly perivascular infiltrate composed of lymphoid cells and plasma cells. Radiographic abnormalities are particularly important, as they are present in up to 95% of symptomatic and 20% of asymptomatic neonates with CS.¹³⁰ Several long bones tend to be affected symmetrically, particularly the lower extremities. The metaphyseal lesions of osteochondritis vary from radiopaque bands to punctate lucencies to mottled regions. Diaphyseal lesions appear as periosteal new bone formation.

Differential diagnosis

As a result of the variable morphology of the lesions and the broad differential diagnosis it engenders, syphilis has been called 'the great imitator.' Blistering in CS must be differentiated from that in other vesiculobullous conditions that involve the palms and soles, including but not limited to congenital candidiasis, acropustulosis of infancy, scabies, and epidermolysis bullosa (see [Chapters 10 and 11](#)). Although unlikely, concern for possible congenital Lyme borreliosis has been described.¹²⁹ However, although Lyme disease can result in a false-positive treponemal test, a nontreponemal VDRL test can be used to differentiate Lyme disease from syphilis because in the former the VDRL test is nonreactive.

Course, management, treatment, and prognosis

If CS is determined, or if there is inadequate maternal and newborn information to confirm appropriate maternal treatment and/or lack of evidence for neonatal infection, then penicillin therapy is recommended. The recommended dose, duration, and route of penicillin administration and follow-up vary according to a combination of specific historical, clinical, and laboratory factors for both the mother and child. Description of these recommendations is beyond the scope of this chapter but is well presented in guidelines published by both

the Centers for Disease Control and Prevention as well as the American Academy of Pediatrics.¹³¹ Importantly, positive MHA-TP and FTA-ABS treponemal tests usually remain reactive for life, despite successful treatment. The prognosis in promptly treated early congenital syphilis is excellent.

MYCOBACTERIUM TUBERCULOSIS

Tuberculosis presenting in the neonatal timeframe can either be congenital (vertically acquired) or postnatally acquired. Although rare, the risk of congenital tuberculosis (CT) increased in the 1990s because of an increase in the number of tuberculosis cases in women of childbearing age. This reflects an increase in the incidence of tuberculosis overall, due in part to the human immunodeficiency virus (HIV) epidemic, as well as increased international adoption and lack of nonemergency medical care to illegal immigrants. The following definition for CT was suggested: presence of proven tuberculous lesions plus one of the following criteria: tuberculous lesions present in the first week of life; a primary hepatic complex or hepatic granulomas; tuberculous infection of the maternal genital tract or placenta; or exclusion of postnatal transmission of tuberculosis by a thorough investigation of contacts.¹³² In practice, distinguishing postnatally acquired tuberculosis from CT is not always possible. Even though the distinction is not important for therapeutic decisions, identification of the person infecting the infant postnatally has important public health implications in attempting to halt the spread of infection in the community.

Cutaneous findings

Cutaneous findings in CT are unusual and include scaly, erythematous, umbilicated papules and subcutaneous nodules.¹³³ Infants with postnatal genital tuberculosis following circumcision may present with firm, nontender, enlarged, inguinal lymph nodes that progress to ulcerated, suppurative, bilateral, inguinal lymphadenopathy with sinus tract formation. Extensive ulceration of the penis and scrotum and varicella-like cutaneous lesions also have been described.¹³⁴

Extracutaneous findings

Newborns with CT are frequently premature and have low birthweight. They may be symptomatic at birth. The symptoms of CT more commonly present during the 2nd to 4th weeks of life with poor feeding, listlessness, respiratory distress, fever, hepatosplenomegaly, abdominal distension, ear discharge, and lymphadenopathy.¹²⁸ Most infected infants have abnormal chest radiographs (e.g., hilar lymphadenopathy, parenchymal infiltrates), and approximately 50% have a miliary pattern. Meningitis is present in about 20% of cases. Infants with postnatally acquired tuberculosis may present with fever, lethargy, respiratory distress, cough, vomiting, weight loss, lymphadenopathy, anemia, and hepatosplenomegaly at 4 weeks to several months after birth.¹³⁵

Etiology and pathogenesis

Tuberculosis can be transmitted from mother to child in utero via hematogenous spread of *Mycobacterium tuberculosis* from the placenta or aspiration of amniotic fluid contaminated from the placenta or an ascending genital infection.¹³² The mother of a child with CT may be completely asymptomatic or may have a range of clinical manifestations for tuberculosis including but

not limited to pleural effusions, meningitis or endometritis. Interestingly, while female genital tuberculosis is rare, acid-fast bacilli can often be identified in the placenta of women with children suffering from CT.¹³¹ Transplacental spread may produce a primary focus of infection in the liver, with involvement of the periportal lymph nodes and secondary hematogenous spread to the lungs, spleen, other viscera, and the central nervous system.¹³² Postnatal transmission is often via exposure of the child to a close contact with active respiratory tuberculosis. Additionally, postnatal exposure can also be from contaminated milk or local infection of compromised skin or mucous membranes. Women with isolated pulmonary tuberculosis are unlikely to infect the infant until after birth. Infection of the skin of the head and neck or the oral mucous membranes, associated with regional lymphadenopathy, may occur by kissing. In the past, tuberculosis of the skin and mucous membranes of the male genitalia was reported 1–4 weeks after ritual circumcision by an infected operator.

Diagnosis

CT should be suspected in any infant who presents with a sepsis-like syndrome, negative bacterial cultures, and lack of response to antibiotic therapy. A thorough history, including information regarding the risks for tuberculosis in the mother and other close contacts is invaluable to improving the time to diagnosis. Diagnosis is confirmed by identification of *M. tuberculosis* in tissue (e.g., liver, lymph node, bone marrow, skin) or fluid from the stomach, trachea, urinary tract, bone marrow, middle ear, or pleural spaces. Culture is the gold standard for identifying *M. tuberculosis* and confirming the diagnosis. However, because *M. tuberculosis* is slow growing, additional testing mechanisms can be helpful to guide initial therapy. Acid-fast stains are helpful if they are positive but a negative acid-fast stain does not rule out the presence of *M. tuberculosis*. False-positive smears from gastric aspirates in a newborn are rare. The use of a DNA probe may allow earlier detection but the accuracy of these probes used directly on specimens obtained from neonates is not well-defined. Other indirect testing modalities such as the Mantoux skin test, performed with 5 TU PPD (tuberculin purified protein derivative) can be done but are not typically clinically useful in this patient population. The PPD is usually initially negative and may take 3 weeks to 3 months to become positive. Interferon gamma release assays may be useful diagnostic tests in this patient population but further evaluation is necessary before they can be routinely endorsed.¹³⁴ The mother of a neonate with suspected tuberculosis should also be evaluated for the presence of tuberculosis. A predelivery history can identify mothers with an increased risk for tuberculosis. If this is the case, the placenta should be examined and cultured at the time of birth.

Course, management, treatment, and prognosis

The course of CT may vary from acute and fulminant to subacute and insidious. Because CT is a relatively rare event, outcome data are limited. However, even with treatment, the case fatality rate of CT is substantial.¹³² Treatment for CT and postnatally acquired disease is the same and should be initiated promptly. A number of factors need to be considered prior to initiating therapy such as location of the infection (pulmonary, extrapulmonary, and central nervous system), regional resistance patterns, and knowledge of isolates previously obtained from the mother or other close contacts. Typically, initial

therapy includes a four-drug regimen. Isoniazid, rifampin, and pyrazinamide make up the back-bone of the four-drug therapy. Options for the fourth agent include ethambutol, ethionamide, or an aminoglycoside (i.e., streptomycin, amikacin, kanamycin, or capreomycin).¹³⁶ Decisions on the initial antibiotic regimen as well as decisions for adjustment in the regimen and total duration of therapy should be made in close concert with an infectious disease specialist with experience in caring for patients with tuberculosis.

Access the full reference list at ExpertConsult.com 

Figures 2 and 15 are online at ExpertConsult.com 

Box 2 is available online at ExpertConsult.com 

KEY REFERENCES

- Larson AA, Dinulos JG. Cutaneous bacterial infections in the newborn. *Curr Opin Pediatr* 2005;17:481–5.
- Hebert AA, Esterly NB. Bacterial and candidal cutaneous infections in the neonate. *Dermatol Clin* 1986;4:3–21.
- Hanakawa Y, Schechter NM, Lin C, et al. Molecular mechanisms of blister formation in bullous impetigo and staphylococcal scalded skin syndrome. *J Clin Invest* 2002;110:53–60.
- Honig PJ, Frieden IJ, Kim HJ, et al. Streptococcal intertrigo: an underrecognized condition in children. *Pediatrics* 2003;112:1427–9.
- Kharazmi SA, Hirsh DA, Simon HK, et al. Management of afebrile neonates with skin and soft tissue infections in the pediatric emergency department. *Pediatr Emerg Care* 2012;28(10):1013–16.
- Chen AE, Carroll KC, Diener-West M, et al. Randomized controlled trial of cephalexin versus clindamycin for uncomplicated pediatric skin infections. *Pediatrics* 2011;127(3):e573–80.
- Liu C. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* 2011;52(3):285–92.
- Fustes-Morales A, Gutierrez-Castrellon P, Duran-Mckinster C, et al. Necrotizing fasciitis: report of 39 pediatric cases. *Arch Dermatol* 2002;138(7):893–9.
- Hsieh WS, Yang PH, Chao HC, et al. Neonatal necrotizing fasciitis: a report of three cases and review of the literature. *Pediatrics* 1999;103(4):e53.
- Saiman L. Strategies for prevention of nosocomial sepsis in the neonatal intensive care unit. *Curr Opin Pediatr* 2006;18(2):101–6.
- Darmstadt GL. Acute infectious purpura fulminans: pathogenesis and medical management. *Pediatr Dermatol* 1998;15:169–83.
- Shwayder T, Akland T. Neonatal skin barrier: structure, function, and disorders. *Dermatol Ther* 2005;18:87–103.
- Centers for Disease Control and Prevention. Toxic shock syndrome. 1997 Case definition. Available at: <http://www.cdc.gov/ncphi/diss/nndss/casedef/toxicss1997.htm>. (Accessed: November 11, 2008).
- Working Group on Severe Streptococcal Infections. Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. *JAMA* 1993;269:390–1.
- American Academy of Pediatrics. Syphilis. In: Pickering LK, Baker CJ, Kimberlin DW, et al, editors. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village: American Academy of Pediatrics; 2012. p. 690–703.

REFERENCES

- Larson AA, Dinulos JG. Cutaneous bacterial infections in the newborn. *Curr Opin Pediatr* 2005;17:481–5.
- Edwards WH, Conner JM, Soll RF. The effect of prophylactic ointment therapy on nosocomial sepsis rates and skin integrity in infants with birth weights of 501 to 1000 g. *Pediatrics* 2004;113(5):1195–203.
- Darmstadt GL, Lane AT. Impetigo: an overview. *Pediatr Dermatol* 1994;11:293–303.
- Leyden JJ, Marples RR, Kligman AM. *Staphylococcus aureus* in the lesions of atopic dermatitis. *Br J Dermatol* 1974;90:525–30.
- Florman AL, Holzman RS. Nosocomial scalded skin syndrome. Ritter's disease caused by phage group 3 *Staphylococcus aureus*. *Am J Dis Child* 1980;134:1043–5.
- Sandhu K, Kanwar AJ. Generalized bullous impetigo in a neonate. *Pediatr Dermatol* 2004;21:667–9.
- Hebert AA, Esterly NB. Bacterial and candidal cutaneous infections in the neonate. *Dermatol Clin* 1986;4:3–21.
- Watkins P. Impetigo: aetiology, complications and treatment options. *Nurs Stand* 2005;19:50–4.
- Hanakawa Y, Schechter NM, Lin C, et al. Molecular mechanisms of blister formation in bullous impetigo and staphylococcal scalded skin syndrome. *J Clin Invest* 2002;110:53–60.
- Yamasaki O, Yamaguchi T, Sugai M, et al. Clinical manifestations of staphylococcal scalded-skin syndrome depend on serotypes of exfoliative toxins. *J Clin Microbiol* 2005;43:1890–3.
- Anari S, Karagama YG, Fulton B, Wilson JA. Neonatal disseminated methicillin-resistant *Staphylococcus aureus* presenting as orbital cellulitis. *J Laryngol Otol* 2005;119:64–7.
- Koning S, van der Wouden JC. Treatment for impetigo. *BMJ* 2004;329:695–6.
- Richter SS, Heilmann KP, Dohrn CL, et al. Activity of ceftaroline and epidemiologic trends in *Staphylococcus aureus* isolates collected from 43 medical centers in the United States in 2009. *Antimicrob Agents Chemother* 2011;55(9):4154–60.
- Regev-Yochay G, Rubinstein E, Barzilai A, et al. Methicillin-resistant *Staphylococcus aureus* in neonatal intensive care unit. *Emerg Infect Dis* 2005;11:453–6.
- Zetola N, Francis JS, Nuermberger EL, et al. Community-acquired methicillin-resistant *Staphylococcus aureus*: an emerging threat. *Lancet Infect Dis* 2005;5:275–86.
- Darmstadt GL. Antibiotics in the management of pediatric skin disease. *Dermatol Clin* 1998;16:509–25.
- Johnston GA. Treatment of bullous impetigo and the staphylococcal scalded skin syndrome in infants. *Expert Rev Anti Infect Ther* 2004;2(3):439–46.
- Healy CM, Hulten KG, Palazzi DL, et al. Emergence of new strains of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Clin Infect Dis* 2004;39:1460–6.
- Honig PJ, Frieden IJ, Kim HJ, et al. Streptococcal intertrigo: an underrecognized condition in children. *Pediatrics* 2003;112:1427–9.
- Janniger CK, Schwartz RA, Szepletowski JC, et al. Intertrigo and common secondary skin infections. *Am Fam Physician* 2005;72:833–8.
- Rehder PA, Eliezer ET, Lane AT. Perianal cellulitis. Cutaneous group A streptococcal disease. *Arch Dermatol* 1988;124(5):702–4.
- Herbst R. Perineal streptococcal dermatitis/disease: recognition and management. *Am J Clin Dermatol* 2003;4(8):555–60.
- Heath C, Desai N, Silverberg NB. Recent microbiological shifts in perianal bacterial dermatitis: *Staphylococcus aureus* predominance. *Pediatr Dermatol* 2009;26(6):696–700.
- Stahelin-Massik J, Gnehm HE, Itin PH. *Pseudomonas folliculitis* in a young child. *Pediatr Infect Dis J* 2000;19(4):362–3.
- Sladden MJ, Johnston GA. More common skin infections in children. *BMJ* 2005;330:1194–8.
- Pollard AJ, Isaacs A, Hermione Lyall EG, et al. Potentially lethal bacterial infection associated with varicella zoster virus. *BMJ* 1996;313:283–5.
- Maguiness SM, Frieden IJ. Current management of infantile hemangiomas. *Semin Cutan Med Surg* 2012;29(2):106–14.
- Wollina U. Acute paronychia: comparative treatment with topical antibiotic alone or in combination with corticosteroid. *J Eur Acad Dermatol Venereol* 2001;15:82–4.
- Brook I. Aerobic and anaerobic microbiology of paronychia. *Ann Emerg Med* 1990;19:994–6.
- Guvenc H, Aygun AD, Yasar F, et al. Omphalitis in term and preterm appropriate for gestational age and small for gestational age infants. *J Trop Pediatr* 1997;43:368–72.
- Manzar S, Nair AK, Pai MG, et al. Omphalitis and necrotizing fasciitis in neonates. *Saudi Med J* 2004;25:2044–5.
- Sawardekar KP. Changing spectrum of neonatal omphalitis. *Pediatr Infect Dis J* 2004;23:22–6.
- Qureshi F, Jacques SM, Bendon RW, et al. *Candida* funisitis: A clinicopathologic study of 32 cases. *Pediatr Dev Pathol* 1998;1(2):118–24.
- Fraser N, Davies BW, Cusack J. Neonatal omphalitis: a review of its serious complications. *Acta Paediatr* 2006;95(5):519–22.
- Ameh EA, Nmadu PT. Major complications of omphalitis in neonates and infants. *Pediatr Surg Int* 2002;18:413–16.
- Sadow KB, Chamberlain JM. Blood cultures in the evaluation of children with cellulitis. *Pediatrics* 1998;101:E4.
- Howe PM, Eduardo Fajardo J, Orcutt MA. Etiologic diagnosis of cellulitis: comparison of aspirates obtained from the leading edge and the point of maximal inflammation. *Pediatr Infect Dis J* 1987;6:685–6.
- Molarte AB, Isenberg SJ. Periorbital cellulitis in infancy. *J Ophthalm Nurs Techn* 1990;9:106–9.
- Cruz AA, Mussi-Pinhata MM, Akaishi PM, et al. Neonatal orbital abscess. *Ophthalmology* 2001;108(12):2316–20.
- Miller A, Castanes M, Yen M, et al. Infantile orbital cellulitis. *Ophthalmology* 2008;115(3):594.
- Howe L, Jones NS. Guidelines for the management of periorbital cellulitis/abscess. *Clin Otolaryngol Allied Sci* 2004;29:725–8.
- Brook I. Microbiology and antimicrobial treatment of orbital and intracranial complications of sinusitis in children and their management. *Int J Pediatr Otorhinol* 2009;73(9):1183–6.
- Emmett Hurley P, Harris GJ. Subperiosteal abscess of the orbit: duration of intravenous antibiotic therapy in nonsurgical cases. *Ophthal Plast Reconstr Surg* 2012;28(1):22–6.
- Dickson SD, Alter SJ. Cutaneous gonococcal abscess of the abdomen in a child. *Pediatr Emerg Care* 2011;27(9):863–4.
- Kharazmi SA, Hirsh DA, Simon HK, et al. Management of afebrile neonates with skin and soft tissue infections in the pediatric emergency department. *Pediatr Emerg Care* 2012;28(10):1013–16.
- Chen AE, Carroll KC, Diener-West M, et al. Randomized controlled trial of cephalexin versus clindamycin for uncomplicated pediatric skin infections. *Pediatrics* 2011;127(3):e573–80.
- Liu C. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clin Infect Dis* 2011;52(3):285–92.
- Stricker T, Navratil F, Sennhauser FH. Mastitis in early infancy. *Acta Paediatr* 2005;94:166–9.
- Brook I. The aerobic and anaerobic microbiology of neonatal breast abscess. *Pediatr Infect Dis J* 1991;10:785–6.
- Sauer MW, Hirsh DA, Simon HK, et al. Pediatric abscess characteristics associated with hospital admission from the ED. *Am J Emerg Med* 2011;29(9):1013–18.
- Stauffer WM, Kamat D. Neonatal mastitis. *Pediatr Emerg Care* 2003;19(3):165–6.
- Cordero L, Anderson CW, Zuspan FP. Scalp abscess: a benign and infrequent complication of fetal monitoring. *Am J Obstet Gynecol* 1983;146:126–30.
- Brook I, Frazier EH. Microbiology of scalp abscess in newborns. *Pediatr Infect Dis J* 1992;11:766–8.
- Weiner EJ, McIntosh MS, Joseph MM, et al. Neonatal scalp abscess: is it a benign disease? *J Emerg Med* 2011;40(5):e97–101.
- Nazir Z. Necrotizing fasciitis in neonates. *Pediatr Surg Int* 2005;21:641–4.
- Fustes-Morales A, Gutierrez-Castrellon P, Duran-Mckinster C, et al. Necrotizing fasciitis: report of 39 pediatric cases. *Arch Dermatol* 2002;138(7):893–9.
- Hsieh WS, Yang PH, Chao HC, et al. Neonatal necrotizing fasciitis: a report of three cases and review of the literature. *Pediatrics* 1999;103(4):e53.
- Liu CT, Chen YC, Chen TH, et al. Necrotizing fasciitis of thigh associated with *Escherichia coli* bacteremia in a patient on chronic hemodialysis. *Hemodial Int* 2012;16(4):564–7.
- Fustes-Morales A, Gutierrez-Castrellon P, Duran-Mckinster C, et al. Necrotizing fasciitis: report of 39 pediatric cases. *Arch Dermatol* 2002;138(7):893–9.
- Eneli I, Davies HD. Epidemiology and outcome of necrotizing fasciitis in children: an active surveillance study of the Canadian Paediatric Surveillance Program. *J Pediatr* 2007;151(1):79–84.
- Gangopadhyay AN, Pandey A, Upadhyay VD, et al. Neonatal necrotizing fasciitis – Varanasi experience. *Int Wound J* 2008;5:108–12.
- Pasternack MS, Swartz MN. Cellulitis, necrotizing fasciitis, and subcutaneous tissue infections. In: Mandell GL, Bennett JE, Dolin R, editors.

- Principles and practice of infectious diseases. 7th ed. Philadelphia: Churchill Livingstone/Elsevier; 2009.
63. Jamal N, Teach SJ. Necrotizing fasciitis. *Pediatr Emerg Care* 2011;27(12):1195–9.
 64. Inoue S, Odaka A, Hashimoto D, et al. Rare case of disseminated neonatal zygomycosis mimicking necrotizing enterocolitis with necrotizing fasciitis. *J Pediatr Surg* 2011;46(10):E29–32.
 65. Lin CY, Hsu CH, Liu KC, et al. Serial immunologic and histopathologic studies in the treatment of necrotizing fasciitis with combined immunodeficiency by a bovine thymic extract (thymostimulin). *J Pediatric Surg* 1986;21(11):1000–4.
 66. Stamenkovic I, Lew PD. Early recognition of potentially fatal necrotizing fasciitis. The use of frozen-section biopsy. *N Engl J Med* 1984;310:1689–93.
 67. Zimbelman J, Palmer A, Todd J. Improved outcome of clindamycin compared with beta-lactam antibiotic treatment for invasive *Streptococcus pyogenes* infection. *Pediatr Infect Dis J* 1999;18(12):1096–100.
 68. Stevens DL, Gibbons AE, Bergstrom R, et al. The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. *J Infect Dis* 1988;158(1):23–8.
 69. Hughes JR, Newbould M, du Vivier AW, et al. Fatal *Pseudomonas* septicemia and vasculitis in a premature infant. *Pediatr Dermatol* 1998;15:122–4.
 70. Reich HL, Williams Fadeyi D, Naik NS, et al. Nonpseudomonal ecthyma gangrenosum. *J Am Acad Dermatol* 2004;50(5 Suppl):S114–17.
 71. Gunes T, Akcakus M, Kurtoglu S, et al. Harlequin baby with ecthyma gangrenosum. *Pediatr Dermatol* 2003;20:529–30.
 72. Patrick CC. Coagulase-negative staphylococci: pathogens with increasing clinical significance. *J Pediatr* 1990;116:497–507.
 73. Hall RT, Hall SL, Barnes WG, et al. Characteristics of coagulase-negative staphylococci from infants with bacteremia. *Pediatr Infect Dis J* 1987;6:377–83.
 74. D'Angio CT, McGowan KL, Baumgart S, et al. Surface colonization with coagulase-negative staphylococci in premature neonates. *J Pediatr* 1989;114:1029–34.
 75. Bjorkqvist M, Jurstrand M, Bodin L, et al. Defective neutrophil oxidative burst in preterm newborns on exposure to coagulase-negative staphylococci. *Pediatr Res* 2004;55:966–71.
 76. Saiman L. Strategies for prevention of nosocomial sepsis in the neonatal intensive care unit. *Curr Opin Pediatr* 2006;18(2):101–6.
 77. Darmstadt GL. Acute infectious purpura fulminans: pathogenesis and medical management. *Pediatr Dermatol* 1998;15:169–83.
 78. Gurgey A, Aytac S, Kanra G, et al. Outcome in children with purpura fulminans: report on 16 patients. *Am J Hematol* 2005;80:20–5.
 79. Wong VK, Hitchcock W, Mason WH. Meningococcal infections in children: a review of 100 cases. *Pediatr Infect Dis J* 1989;8:224–7.
 80. van Deuren M, van Dijke BJ, Koopman RJ, et al. Rapid diagnosis of acute meningococcal infections by needle aspiration or biopsy of skin lesions. *BMJ* 1993;306:1229–32.
 81. Periappuram M, Taylor MR, Keane CT. Rapid detection of meningococci from petechiae in acute meningococcal infection. *J Infect* 1995;31:201–3.
 82. Adcock DM, Hicks MJ. Dermatopathology of skin necrosis associated with purpura fulminans. *Semin Thromb Hemost* 1990;16:283–92.
 83. Ezer U, Misirlioglu ED, Colba V, et al. Neonatal purpura fulminans due to homozygous protein C deficiency. *Pediatr Hematol Oncol* 2001;18:453–8.
 84. Katier N, Traen M, De Dooy J, et al. Neonatal purpura due to *Neisseria meningitidis* serogroup C infection. *Eur J Pediatr* 2003;162:283–4.
 85. Brandtzaeg P, van Deuren M. Meningococcal infections at the start of the 21st century. *Adv Pediatr* 2005;52:129–62.
 86. Leclerc F, Noizet O, Dorkenoo A, et al. Treatment of meningococcal purpura fulminans. *Arch Pediatr* 2001;8:S677–88.
 87. American Academy of Pediatrics. Meningococcal infections. In: Pickering LK, Baker CJ, Kimberlin DW, et al, editors. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village: American Academy of Pediatrics; 2012. p. 500–9.
 88. Shwayder T, Akland T. Neonatal skin barrier: structure, function, and disorders. *Dermatol Ther* 2005;18:87–103.
 89. Saiman L, Jakob K, Holmes KW, et al. Molecular epidemiology of staphylococcal scalded skin syndrome in premature infants. *Pediatr Infect Dis J* 1998;17:329–34.
 90. Melish ME, Glasgow LA. Staphylococcal scalded skin syndrome: the expanded clinical syndrome. *J Pediatr* 1971;78:958–67.
 91. Raymond J, Bingen E, Brahimi N, et al. Staphylococcal scalded skin syndrome in a neonate. *Eur J Clin Microbiol Infect Dis* 1997;16:453–4.
 92. Amagai M, Matsuyoshi N, Wang ZH, et al. Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1. *Nature Med* 2000;6:1275–7.
 93. Amagai M, Yamaguchi T, Hanakawa Y, et al. Staphylococcal exfoliative toxin B specifically cleaves desmoglein 1. *J Invest Dermatol* 2002;118:845–50.
 94. Chuang YY, Huang YC, Lin TY. Toxic shock syndrome in children: epidemiology, pathogenesis, and management. *Paediatr Drugs* 2005;7:11–25.
 95. Hajjeh RA, Reingold A, Weil A, et al. Toxic shock syndrome in the United States: surveillance update, 1979–1996. *Emerg Infect Dis* 1999;5(6):807–10.
 96. Frame JD, Eve MD, Hackett ME, et al. The toxic shock syndrome in burned children. *Burns Incl Them Inj* 1985;11(4):234–41.
 97. DeVries AS, Leshner L, Schlievert PM, et al. Staphylococcal toxic shock syndrome 2000–2006: Epidemiology, clinical features, and molecular characteristics. *PLoS One* 2011;6(8):e22997.
 98. Stevens DL. Invasive group A streptococcal disease. *Infect Agents Dis* 1996;5:157–66.
 99. Belani K, Schlievert PM, Kaplan EL, et al. Association of exotoxin-producing group A streptococci and severe disease in children. *Pediatr Infect Dis J* 1991;10:351–4.
 100. Stevens DL. Streptococcal toxic-shock syndrome: spectrum of disease, pathogenesis, and new concepts in treatment. *Emerg Infect Dis* 1995;1:69–78.
 101. Wolf JE, Rabinowitz LG. Streptococcal toxic shock-like syndrome. *Arch Dermatol* 1995;131:73–7.
 102. Stevens DL, Tanner MH, Winship J, et al. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. *N Engl J Med* 1989;321:1–7.
 103. Centers for Disease Control and Prevention. Toxic shock syndrome. 1997 Case definition. Available at: <http://wwwn.cdc.gov/NNDSS/script/casedef.aspx?CondYrID=868&DatePub=1/1/1997%2012:00:00%20AM>. (Accessed February 2014).
 104. Working Group on Severe Streptococcal Infections. Defining the group A streptococcal toxic shock syndrome. Rationale and consensus definition. *JAMA* 1993;269:390–1.
 105. Bisno AL, Stevens DL. Streptococcal infections of skin and soft tissues. *N Engl J Med* 1996;334:240–5.
 106. Lopez JB, Gross P, Boggs TR. Skin lesions in association with beta-hemolytic *Streptococcus* group B. *Pediatrics* 1976;58:859–61.
 107. Baker CJ. Group B streptococcal cellulitis-adenitis in infants. *Am J Dis Child* 1982;136:631–3.
 108. Kline A, O'Donnell E. Group B *Streptococcus* as a cause of neonatal bullous skin lesions. *Pediatr Infect Dis J* 1993;12(2):165–6.
 109. Shet A, Ferrieri P. Neonatal and maternal group B streptococcal infections: a comprehensive review. *Indian J Med Res* 2004;120:141–50.
 110. Gibbs RS, Schrag S, Schuchat A. Perinatal infections due to group B streptococci. *Obstet Gynecol* 2004;104:1062–76.
 111. Rand TH. Group B streptococcal cellulitis in infants: a disease modified by prior antibiotic therapy or hospitalization? *Pediatrics* 1988;81:63–5.
 112. El Beitune P, Duarte G, Maffei CM. Colonization by *Streptococcus agalactiae* during pregnancy: maternal and perinatal prognosis. *Brazil J Infect Dis* 2005;9:276–82.
 113. Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. *Obstet Gynecol Surv* 2005;60:637–9.
 114. Heath PT. An update on vaccination against group B *Streptococcus*. *Expert Rev Vaccines* 2011;10(5):685–94.
 115. Greenhow TL, Hung YY, Herz AM. Changing epidemiology of bacteremia in infants aged 1 week to 3 months. *Pediatrics* 2012;129(3):e590–6.
 116. Posfay-barbe KM, Wald ER. Seminars in fetal neonatal medicine. *Listeriosis* 2009;14(4):228–33.
 117. Smith KJ, Yeager J, Skelton HG 3rd, et al. Diffuse petechial pustular lesions in a newborn. Disseminated *Listeria monocytogenes*. *Arch Dermatol* 1994;130:245, 248.
 118. Evans JR, Allen AC, Stinson DA, et al. Perinatal listeriosis: report of an outbreak. *Pediatr Infect Dis* 1985;4:237–41.
 119. McLauchlin J. Human listeriosis in Britain, 1967–1985, a summary of 722 cases. 1. Listeriosis during pregnancy and in the newborn. *Epidemiol Infect* 1990;104:181–9.
 120. Espaze EP, Reynaud AE. Antibiotic susceptibilities of *Listeria*: in vitro studies. *Infection* 1988;16:S160–4.
 121. Miller R, Karras DJ. Commentary. Update on emerging infections: news from the Centers for Disease Control and Prevention. Congenital syphilis – United States 2003–2008. *Ann Emerg Med* 2010;56(3):296–7.

122. Centers for Disease Control and Prevention (CDC). Congenital syphilis – United States, 2002. *MMWR Morb Mortal Wkly Rep* 2004;53(31):716–19.
123. Chawla V, Pandit PB, Nkrumah FK. Congenital syphilis in the newborn. *Arch Dis Child* 1988;63:1393–4.
124. Wendel GD. Gestational and congenital syphilis. *Clin Perinatol* 1988;15:287–303.
125. Evans HE, Frenkel LD. Congenital syphilis. *Clin Perinatol* 1994;21:149–62.
126. Woods CR. Syphilis in children: congenital and acquired. *Semin Pediatr Infect Dis* 2005;16:245–57.
127. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010;59(RR-12):1–110.
128. Sanchez PJ. Laboratory tests for congenital syphilis. *Pediatr Infect Dis J* 1998;17:70–1.
129. Trevisan G, Stinco G, Cinco M. Neonatal skin lesions due to a spirochetal infection: a case of congenital Lyme borreliosis? *Int J Dermatol* 1997;36:677–80.
130. Brion LP, Manuli M, Rai B, et al. Long-bone radiographic abnormalities as a sign of active congenital syphilis in asymptomatic newborns. *Pediatrics* 1991;88:1037–40.
131. American Academy of Pediatrics. Syphilis. In: Pickering LK, Baker CJ, Kimberlin DW, et al, editors. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village: American Academy of Pediatrics; 2012. p. 690–703.
132. Cantwell MF, Shehab ZM, Costello AM, et al. Brief report: congenital tuberculosis. *N Engl J Med* 1994;330:1051–4.
133. McCray MK, Esterly NB. Cutaneous eruptions in congenital tuberculosis. *Arch Dermatol* 1981;117:460–4.
134. De Lauzanne A, Gourgouillon N, Guérin-El Khourouj V, et al. Interferon-gamma release assay performance for diagnosing tuberculosis disease in 0- to 5-year-old children. *Pediatr Infect Dis J* 2011;30(11):995–7.
135. Kendig EL Jr. Tuberculosis in the very young; report of three cases in infants less than one month of age. *Am Rev Tuberc* 1954;70:161–5.
136. American Academy of Pediatrics. Tuberculosis. In: Pickering LK, Baker CJ, Kimberlin DW, et al, editors. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village: American Academy of Pediatrics; 2012. p. 736–59.

Introduction

Viral infections can induce a remarkable variety of cutaneous manifestations in the neonate and toddler. The clinical manifestations of any viral infection are influenced by the virulence, tissue tropism, and age at which the infection is acquired. Infections may occur in utero, perinatally (acquired between the onset of labor and the delivery), or postnatally. Skin findings may be a result of local invasion and infection, or an indirect result of viral infection of other tissues. Diagnosis of infection is based on the morphology and distribution of the skin lesions, as well as the overall clinical presentation, supported by specific laboratory studies when possible. Rapid diagnosis and appropriate antiviral therapy maximize the possibility of a positive outcome for the infant.

Herpes simplex virus

Herpes simplex virus (HSV) types 1 and 2 are pathogens for the fetus, newborn, infant and toddler, which induce a spectrum of clinical disease. Specific manifestations depend on the time and route of exposure as well as maternal immune status (primary vs recurrent maternal infection). HSV is a large, double-stranded DNA virus that can produce an acute primary infection in the susceptible host. In addition, HSV-1 and -2, like other herpes viruses, have the ability to integrate into host DNA and establish latency. Poorly understood host and environmental factors can cause reactivation of virus within latently infected sensory ganglia, leading to recurrent, active infections. Neonatal infection occurs most often as a direct result of active maternal infection, usually from primary infection acquired during pregnancy. The rate of neonatal disease has been shown to parallel the rate of genital herpes in a community.¹

Epidemiology

Neonatal infection is estimated to occur at a rate of 1 in 3000 to 1 in 20 000 live births. Infection of the fetus or newborn may occur during gestation (in utero), at the time of labor and delivery (perinatally), or following the delivery (postnatally). Although the majority of neonatal infections (80–90%) are considered to be acquired perinatally, both in utero infections (4%) and postnatal infections (10%) have been well documented.²

Most affected neonates acquire infection through contact with infectious genital secretions or herpetic lesions at the time of vaginal delivery. Although primary infection in the pregnant woman usually leads to symptomatic illness, a significant proportion of women with primary infection do not have recognizable systemic or local disease.³ Primary maternal infection is usually associated with prolonged shedding (2–3 weeks) of high titers of virus from lesions, while the maternal immune response

develops, in contrast to the more limited viral shedding and much shorter duration of lesions (2–5 days) with recurrent disease in women with specific humoral and cellular immunity. Neonatal infection occurs in up to 50% of infants born to mothers during primary infection, compared with an estimated 2% or less of infants born to mothers suffering from recurrent infection; pre-existing protective maternal antibodies likely explain this difference in clinical outcome. Active maternal infection at the time of delivery, based on viral culture, is thought to occur in approximately 1–7 per 1000 births.⁴ However, data based on polymerase chain reaction (PCR) techniques from genital specimens at delivery suggest that active maternal infection may occur up to eight times more frequently than previously appreciated.⁵ Prospective studies have documented that the majority of women with active infection at the time of delivery are asymptomatic, suggesting that improved rapid laboratory diagnosis and careful examination are needed to identify the at-risk mother and infant.

The optimal strategy for preventing neonatal HSV infection is controversial. Discordant HSV status of sexual partners is a risk factor if the female is susceptible, and queries regarding partner status and advice regarding abstinence near term for susceptible women with infected partners are appropriate. Routine HSV screening in pregnant women and antepartum HSV cultures in asymptomatic women with history of recurrent disease are not recommended. Based on evaluation of available limited or inconsistent scientific evidence (Level B), the American College of Obstetrics and Gynecology recommends that women with active recurrent genital herpes should be offered suppressive viral therapy at or beyond 36 weeks' gestation and that cesarean delivery is indicated in women with active genital lesions or prodromal symptoms (e.g., vulvar pain or burning) at the time of delivery.⁶ Cesarean delivery is not recommended for women with a history of HSV who do not have active disease or have only non-genital disease at the time of delivery. Importantly, neonatal herpes infection has been described in infants born to mothers taking antiviral suppressive therapy and such cases may present with an atypical clinical picture and/or viral resistance patterns.^{2,7}

Postnatal infections may be transmitted from both maternal, non-genital sites (including breast lesions) and non-maternal sources, such as other family members or nosocomial transmission from healthcare workers. In the absence of an HSV lesion on the breast, breast-feeding is not contraindicated. Active handwashing and awareness of transmission risk should be employed by all individuals with a history of or active HSV who are in contact with an infant.

INTRAUTERINE HSV INFECTION

Congenital (intrauterine) infection was described in 1966 by Sieber and colleagues, in an infant with culture-positive lesions,

seizures, and evidence of immunity at the time of a normal delivery in which the amniotic membranes were ruptured at birth.⁸ In 1969, South described an infant with microcephaly, microphthalmia, seizures, and vesicular lesions on the fingers and toes following a maternal primary HSV-2 genital infection during the first month of pregnancy.⁹ Subsequent studies of congenital infection have documented the presence of specific cell-mediated immunity to HSV in the newborn at birth, whereas infants infected during labor and delivery do not usually develop cellular immunity until the second week of the infection.¹⁰

Infection in utero may occur either as a result of ascending infection through apparently intact membranes, or as a result of viremia occurring with a primary maternal infection. Fetal infection often leads to fetal death; however, if the fetus survives, delivery may occur at term with late sequelae in both skin and central nervous system (CNS).

Cutaneous findings

Skin manifestations at delivery are the result of residua from primary fetal infection in addition to latent virus reactivation at previous cutaneous sites of fetal infection. Skin lesions are common in the neonatal period (Fig. 13.1). In one study, 70% of infected infants had vesicular lesions, and 30% also had evidence of scar formation on the face, trunk, or extremities.¹¹ In addition, aplasia cutis congenita-like skin findings and lesions characteristic of epidermolysis bullosa have been described.¹² Atrophic limbs, previously reported with congenital varicella virus infection, have also been documented with congenital HSV infection.¹³

Extracutaneous findings

HSV infections acquired in utero in which the infant completes a normal gestation are almost invariably associated with CNS damage, which is easily detected by computed tomography (CT). CNS changes indicate longstanding destruction of neuronal tissue without acute inflammation. Microcephaly is present in over 50%, and chorioretinitis is present in 60% of infants with congenital HSV infection. Although skin and CNS abnormalities are present at birth, infected infants often do not show the signs of systemic toxicity and overwhelming sepsis that may occur with primary perinatal or postnatal infection.



Figure 13.1 Congenital herpes simplex. Generalized necrotic crusted papules.

NEONATAL (PERINATAL) HERPES SIMPLEX INFECTION

Neonatal disease occurs in three clinically recognized syndromes, all acquired in the perinatal period: infection localized to the skin, eyes, or mouth (SEM disease); disseminated infection; and CNS infection. Exposure to maternal primary infection at the time of delivery may lead to overwhelming infection in the neonate, with a high mortality rate, or a more slowly progressive, insidious disease in which the infant has only mucocutaneous manifestations or develops slowly progressive neurologic symptoms. The incubation period varies substantially, from clinical symptoms at delivery due to presumed ascending infection through non-intact membranes, to infection presenting as late as 6 weeks of age. Infants with disseminated and SEM disease have an earlier onset, typically presenting between the first and second weeks of life. The variability of the incubation period is dependent on the integrity of the amniotic membranes, the inoculum of virus, the tissue inoculated (e.g., skin, mucous membrane), and the presence or absence of transplacental specific antibody.

Cutaneous findings

Cutaneous or mucosal lesions (mouth, nose, eye) can occur with or without signs of sepsis or encephalitis. Infants with skin, eye, or mouth disease account for 40% of all neonatal cases of HSV infection. The skin lesions appear as small, 2–4 mm vesicles, with surrounding erythema, often in herpetiform (zosteriform) clusters (Fig. 13.2). They usually occur on the part of the body which was in prolonged contact with the cervix. Often, lesions will occur at sites where the skin integrity has been breached. One of the most common sites of cutaneous infection is on the scalp vertex at the site of placement of fetal scalp monitor electrodes (Fig. 13.3). Vesicular lesions usually develop within the first 1–2 weeks of life following inoculation at this site. Lesions may progress locally, or disseminate (Fig. 13.4). In areas of mucosal involvement, a shallow ulceration with moderate inflammation is most often seen. The ulceration may be focal, with the lesion size closely resembling that of a cutaneous vesicle, or ulcerations may spread irregularly, coalescing over a much larger area. Lesions tend to follow the clinical stages of vesicle resolution seen in the older child, with pustulation



Figure 13.2 Neonatal herpes simplex. Cluster of vesicles on the forehead and periocular area.



Figure 13.3 Neonatal herpes simplex. Vesicles with central necrotic plaque at site of fetal monitor electrode placement.



Figure 13.4 Neonatal herpes simplex virus. Multiple vesicles and crusted papules on an erythematous base in the periumbilical area and left flank.

24–72 h after the appearance of the vesicle, followed by eschar formation. Skin lesions are present in most neonates with disseminated disease (77%), and in 60% of infants who present with CNS disease. In any newborn with skin or mucosal lesions of HSV, even without a history of symptomatic illness, an investigation must be undertaken to rule out disseminated or CNS disease.

Extracutaneous findings

HSV dissemination is the most devastating manifestation, presenting in the more premature infant (average gestational age at birth of 36.5 weeks) at an average chronologic age of 11 days. Multisystem involvement is analogous to overwhelming bacterial sepsis. Shock, disseminated intravascular coagulation, and multiple organ system failure are characteristic. Involvement of the lung, liver, and brain is common. The mortality rate is high. Without antiviral therapy, approximately 75% of infants will die, and even with specific antiviral therapy, mortality is still significant. Neurologic sequelae in survivors are also common, occurring in approximately 40%. Statistically, these infants have the lowest average circulating concentration of antibody to HSV.

In as many as 40% of infants ultimately diagnosed with disseminated or CNS infection, clinical disease begins with skin

lesions only. Clinical and laboratory evidence of dissemination or CNS involvement not obvious at the time of presentation may develop during the first days of treatment, despite antiviral therapy.

Infants with HSV encephalitis present at a slightly older age (mean 17 days) and tend to be full term, in contrast with newborns with other clinical presentations. Antibody titers are higher in this group, leading to speculation that antibody may modify the progression of disease, with virus inoculated at delivery producing a clinically undetectable initial infection which spreads from mucosal sites to the CNS. Subtle neurologic symptoms are often present for days before the parent recognizes that the infant requires medical attention. As the child becomes more irritable and seizures become more pronounced, infants are hospitalized and evaluated. Skin lesions are only present in 60% of infants with HSV encephalitis, making the diagnosis difficult in many.

Diagnosis

The diagnosis of a herpes virus infection can be made in several ways (Table 13.1). HSV grows rapidly and easily in cell culture, and evidence of infection may be evident within the first few days after inoculation. Culture remains the most accurate means of diagnosis, but adjunctive tests may provide more rapid results. All suspected cases should have the following samples collected: (1) swab specimens from mouth, nasopharynx, conjunctiva and anus for HSV culture (the same swab can be used to test all sites, ending with the anus); (2) skin vesicle and CSF for PCR and culture analysis; (3) whole blood sample for PCR; and (4) blood sample for ALT testing. The most rapid results can be obtained from scraping of a vesicle sent for histopathologic Tzanck smear analysis, but this test is probably the most unreliable due to interpreter variability and sampling error. Direct fluorescent antibody testing (DFA) is rapid and specific, but not as sensitive as culture. CNS evaluation is necessary to rule out encephalitis. This includes traditional CSF analysis, as well as PCR. CT of the brain may be helpful in the diagnosis of encephalitis but is not considered sensitive until after 5 days of CNS symptoms. Magnetic resonance imaging (MRI) is more sensitive for CNS inflammation of the temporal lobes – the preferred sites of viral replication – and may be diagnostic within 3 days of onset of symptoms. EEG can also be helpful in CNS infections localized to the temporal lobe and may be positive earlier than any imaging study.

Differential diagnosis

Disseminated infection with HSV produces a clinical picture similar to that of early-onset neonatal sepsis caused by group B *Streptococcus*, enteric Gram-negative bacilli, and *Listeria*. Empiric therapy with antibiotics (standard management for the hospitalized ill neonate) will have no effect on the progression of HSV disease. For infants with progressive clinical symptoms of sepsis and sterile bacterial cultures of blood, urine, and CSF, HSV should be considered as a potential pathogen.

Other viral infections in the newborn period may also be confused with HSV. Enteroviral infection can cause a wide spectrum of clinical signs in the neonate, from fever and irritability to overwhelming sepsis with multiple organ system failure, to aseptic meningoencephalitis with minimal symptoms of systemic toxicity. Enteroviral infections may be associated with cutaneous vesiculopustular lesions. Neonatal seizures caused by enteroviral infections are the result of diffuse CNS irritation,

TABLE
13.1

Diagnosis of infection

Virus	Culture	Histology of skin lesion	PCR ^a	Serology
HSV	Widely available and reliable; culture skin lesions, eyes, mouth, CSF, rectum; recommend setting up culture promptly after obtaining specimen	Tzanck stain of epithelial cells from the base of a vesicle is specific for alpha herpesviruses HSV and VZV; direct fluorescent antibody stains for HSV 1 or 2 are specific; DFA stains are specific and sensitive	Highly sensitive; best studied on CSF (sensitivity of skin lesions not well studied); plasma HSV PCR available in some centers	Rising antibody titer to HSV IgG is a sensitive and specific test; HSV IgM is not a sensitive test in the newborn
VZV	Available in many reference laboratories; culture skin lesions; recommend setting up culture promptly after obtaining specimen	Tzanck stain (see above): specific stains available for VZV	Highly sensitive, but not well studied on skin lesions; not widely available	Rising antibody titer to VSV IgG is a sensitive and specific test; VZV IgM is not a sensitive test in the newborn
CMV	Widely available; reliable; culture urine, saliva; urine shell vial culture technique yields results in 48–72 h	Skin lesions are due to extramedullary hematopoiesis, not due to viral replication in skin	Highly sensitive; well studied in plasma as a marker of disseminated CMV infection in immunocompromised hosts	Rising antibody titer to CMV IgG is a sensitive and specific test; CMV IgM is not a sensitive test in the newborn; serologies are rarely used to diagnose neonatal CMV
Rubella	Not usually available; culture pharynx respiratory secretions, CSF, tissue	Skin lesions are due to extramedullary hematopoiesis, not due to viral replication in skin	Not well studied	Rising antibody titer to rubella IgG is a sensitive and specific test; rubella IgM is not a sensitive test in the newborn. Compare mother's prenatal serology test results with those of the infant at the time of birth
Enterovirus	Widely available in viral culture laboratories; culture vesicular lesions, pharynx (during the acute phase of illness), and stool (up to 6 weeks following the illness); some strains including coxsackie virus A6 may be difficult to culture	Nonspecific	Highly sensitive; widely available	Usually not helpful
Parvovirus B19	Not available in standard cell culture	Placental and fetal tissues – intranuclear inclusions in nucleated erythroid cells; EM and immunohistochemistry may be helpful	Highly sensitive; can be used on amniotic fluid, fetal plasma and tissues	IgM or IgG seroconversion helpful in pregnant female. Fetal IgM specific but not sensitive
HIV	Available; not highly sensitive in newborn; not recommended	Nonspecific	Sensitive means of diagnosis, can be repeated at 1–2 months and 4–6 months of age as needed; plasma PCR is the preferred test for infants <12 months of age	Maternal antibody present at birth may persist, especially under 4–6 months and up to 18 months; serologic testing may be most helpful after 12–18 months of age

^aViral PCR panels are available in some centers and PCR diagnostic technology is rapidly evolving.

in contrast to the focal temporal lesions of early HSV disease. Destructive changes of HSV that are appreciated on serial imaging studies of the CNS (by either CT or MRI) are not generally seen with enteroviral disease.

Perinatal varicella may produce overwhelming sepsis in the newborn. The density of cutaneous lesions in neonatal varicella usually far exceeds that seen with HSV infections, which characteristically produce a focal cluster of lesions at the site of inoculation with minimal cutaneous dissemination. However, both demonstrate the identical findings of multinucleate giant

cells on Tzanck preparations. Only virus-specific staining techniques, PCR, or culture will be able to differentiate between these viruses.

Other viral pathogens occasionally cause severe acute disease in the newborn, including influenza A and B, parainfluenza 1, 2, and 3, and adenovirus. In general, the seasonal context of the infection, exposure history, and a predominance of respiratory tract symptoms help differentiate these infections. Viral cultures of the respiratory tract will assist in the identification of these pathogens.

Incontinentia pigmenti may present with localized vesicles, which may be mistaken for herpes simplex infections. These infants often have peripheral eosinophilia. Biopsy will reveal increased numbers of eosinophils, and cultures will be negative for HSV. Vesicular lesions that appear herpetic can also occur in Langerhans' cell histiocytosis. Tzanck preparation will reveal histiocytes, and biopsy will show large numbers of histiocytes and an absence of multinucleate giant cells. Additionally, epidermolytic hyperkeratosis (EHK), epidermolysis bullosa (EB), congenital erosive and vesicular dermatosis, and ankyloblepharon-ectodermal dysplasia clefting syndrome can present with denuded eroded skin and bullae which may be confused with HSV.

Management and prognosis

The treatment of choice in neonatal herpes infections is acyclovir administered intravenously, regardless of the clinical presentation (Table 13.2). Acyclovir 60 mg/kg per day in three divided doses should be given for 14 days for SEM, and for a minimum of 21 days in those with disseminated or CNS disease.¹⁴ In infants with renal failure, the doses should be reduced accordingly. The mortality rate for disseminated disease is about 29%, even with therapy. Approximately 50% of infants will experience cutaneous recurrences. Daily suppressive doses of oral acyclovir have been recommended to prevent skin recurrences and, in infants with CNS disease surviving neonatal HSV, treatment with suppressive doses of oral acyclovir for 6 months after the initial 14–21 day parenteral acyclovir regimen led to improved neurodevelopmental outcomes at 1 year of age.¹⁵ Valacyclovir is also efficacious in the treatment of HSV, but no oral liquid formulation currently exists. Pharmacokinetic studies have shown inter-infant drug clearance variability in those less than 3 months of age, and some experts therefore do not recommend use in very young infants.¹⁶

HSV IN CHILDREN BEYOND THE NEONATAL PERIOD

At least 25% of US children have serologic evidence of HSV-1 by age 7 years. HSV infections in young children may present with clusters of erosions and vesicles (Fig. 13.5). However, most primary, non-neonatal HSV infections are asymptomatic. Gingivostomatitis secondary to HSV-1 is the most common



Figure 13.5 Herpes simplex in an infant. Grouped vesicles and round erosions. In this case, crusting mimics impetigo.

presentation in childhood, generally occurring from 1 to 5 years of age. Children may be quite ill, with fever, drooling, submandibular adenopathy, and diffuse edema and erythema of the gingiva and oral mucous membranes. Extension of lesions to the lips, chin and cheeks often occurs. Ulcers, erosions, and oral symptoms can be so severe that hospitalization may be required for intravenous hydration support. The differential diagnosis includes coxsackie virus infection, Stevens–Johnson disease, and aphthous ulcers.

Isolated HSV labialis may also occur, but less frequently. HSV infection of the pulp of the distal phalanx of a digit, termed herpetic whitlow can occur in children as an isolated finding. Such lesions are slate-gray, vesicular, and painful (Fig. 13.6). They may result from autoinoculation or inoculation from another infected individual. Genital lesions can also occur in young children with vesicular and eroded lesions, but should always raise concern for sexual abuse.

ECZEMA HERPETICUM

This form of severe HSV cutaneous infection develops in individuals who suffer from a chronic skin condition. Though most commonly seen in association with atopic dermatitis, it can be associated with disorders such as Darier disease or pemphigus vulgaris. Patients develop vesiculations and erosions predominantly in affected dermatitis sites where the skin barrier is presumably impaired and more vulnerable to viral invasion. The lesions often have a 'punched-out' monomorphous appearance, and vesicles may not be evident (Fig. 13.7). These children may have high fevers and appear ill. Secondary bacterial infection of the skin and keratoconjunctivitis may also develop. The differential diagnosis includes varicella infections, including zoster, and secondary bacterial infection of primary skin conditions. Families should be counseled regarding the risk of recurrence, and the need to protect their child from direct exposure to active herpes lesions in others.

Therapy of HSV infections in children depends on the severity of involvement and underlying immune considerations.



Figure 13.7 Eczema herpeticum. Numerous monomorphous round erythematous erosions, coalescing into large irregular erosions with crusting.



Figure 13.6 Herpetic whitlow in an infant. Thumb with coalescent vesicles on erythematous base.

TABLE
13.2

Herpes virus infections in neonates and infants

Herpes virus	Age at infection	Clinical findings	Treatment ^a
HSV	Intrauterine	Congenital HSV	
		SKIN LESIONS Vesicles (~70%), scar-like lesions (~30%), reports of lesions concerning for epidermolysis bullosa or aplasia cutis congenita	Parenteral acyclovir 60 mg/kg per day divided three times daily ×21 days (minimum)
		ASSOCIATED ABNORMALITIES Atrophic limbs, microcephaly (~50%), chorioretinitis (~40%)	
	Neonatal/perinatal	SEM disease	
		Infection localized to the skin, eyes, or mouth	Parenteral acyclovir 60 mg/kg per day divided three times daily ×14 days; if ocular involvement: add ophthalmic antiviral (1% trifluridine, 0.1% iododeoxyuridine, or 3% vidarabine)
		SKIN LESIONS Vesicles (2–4 mm), with surrounding erythema, often in herpetiform (zosteriform) clusters; mucosal ulcerations, small and round (2–4 mm) or large and irregular	
		Disseminated infection; CNS infection	
		SKIN LESIONS Vesicles and/or erosions described above may or may not be found	Parenteral acyclovir 60 mg/kg per day divided three times daily ×21 days (minimum)
		SYSTEMIC FINDINGS Septic shock, disseminated intravascular coagulation, multiple organ system failure, seizures	
VZV	Intrauterine	Fetal varicella syndrome/varicella embryopathy	Prevention
		See Table 13.3, Features of fetal varicella syndrome	Vaccination of women prior to childbearing; treatment of exposed, susceptible pregnant women with VZIG as soon as possible (within 48 and up to 96 h after exposure); consideration of treatment of pregnant woman with acyclovir
			Care of affected infant
			Supportive
	Neonatal/perinatal	Neonatal varicella	Prevention
		SKIN LESIONS Variable; red macules which mature into small vesicles; hemorrhagic and/or necrotic vesicles	Neonates born to mothers who have developed varicella from 5 days before to 2 days after delivery should receive VZIG intramuscularly as soon as possible after delivery
			Treatment
			Parenteral acyclovir, 60 mg/kg per day divided three times daily ×10–21 days
	Infant (1–23 months)	Infantile herpes zoster	
		SKIN LESIONS Grouped erythematous papules that vesiculate and crust in a dermatomal distribution	Acyclovir 20 mg/kg per dose by mouth 4 times daily ×10 days
		Infantile varicella	
		SKIN LESIONS Crops of vesicles on erythematous bases 'dewdrop on a rose petal' in different stages	HEALTHY CHILDREN Supportive care
		ASSOCIATED FINDINGS Fever, headache, myalgias	IMMUNOCOMPROMISED CHILDREN Intravenous acyclovir should be started within 24–72 h (<1 year of age, 30 mg/kg per day divided every 8 h for 7–10 days; >1 year of age, 1500 mg/m ² per day divided every 8 h ×7–10 days).
			VZV EXPOSURE OF IMMUNOCOMPROMISED PATIENTS VZIG should be administered within 48 h of exposure (may be given up to 96 h)

^aAdapted from Red Book: 2012 Report of the Committee on Infectious Disease, American Academy of Pediatrics, 2012.

Immunocompromised children and those with eczema herpeticum will often benefit from intravenous therapy. Bland emollients are also often utilized; in children with eczema herpeticum, topical corticosteroids are then added once the infection appears to be responding to antiviral therapy. Most other conditions can be treated with oral therapy if treatment is desired.

Varicella

Varicella (chickenpox) is usually a benign, self-limited disease when it occurs in immunocompetent individuals during childhood. The developing fetus and neonate, however, are at higher risk for an adverse outcome following infection. Fortunately, more than 90% of women are estimated to have varicella zoster virus (VZV) IgG seropositive status, thereby conferring immunity to the fetus. In addition, women planning conception are encouraged to seek VZV vaccination if they do not have evidence of prior immunity, substantially decreasing the risk of fetal infection. The widespread use of the varicella live attenuated (Oka/Merck) vaccine has led to a lower incidence of VZV disease in the general population, thereby decreasing the exposure risk to expectant mothers and infants. However, the vaccine is not 100% effective, and healthcare practitioners must be aware of the possible manifestations of varicella infection in neonates, as well as appropriate therapy.

The exact incidence of varicella during pregnancy is unknown, but is estimated to be between three and 10 cases per 10 000 pregnancies. Fetal or early neonatal exposure may result in a variety of manifestations, ranging from minimal cutaneous lesions to significant morbidity and death. Three distinct disorders may occur following intrauterine or neonatal exposure to VZV: fetal varicella syndrome, neonatal varicella, and infantile herpes zoster.

FETAL VARICELLA SYNDROME

Congenital defects predominantly involving the skin, nervous system, and musculoskeletal system can occur following fetal exposure to varicella virus. Other terms for the fetal varicella syndrome include varicella embryopathy and congenital varicella syndrome.

Cutaneous findings

Specific anomalies include cicatricial skin lesions that correspond to a dermatomal distribution, often with hypoplasia of underlying tissues. These lesions may initially appear as denuded areas and subsequently develop stellate or angular scars (Fig. 13.8).

Extracutaneous findings

Low birthweight is a common finding in affected infants. The varied extracutaneous manifestations of this syndrome can be grouped as neurologic, musculoskeletal, ophthalmologic, gastrointestinal, and genitourinary. Limb paresis and hypoplasia of the extremities are common findings, as is chorioretinitis. Less common findings include microphthalmia, cataracts, nystagmus, hydrocephalus, and mental retardation (Table 13.3).

Etiology and pathogenesis

Varicella zoster virus (VZV) is a herpes virus consisting of double-stranded DNA. The incubation period is usually 14 days, but ranges from 10 to 21 days after exposure. Most fetuses



Figure 13.8 Congenital varicella. Segmental and stellate deep scars on the right ear, head, shoulder, and arm, which appear to follow a dermatome.

exposed to VZV during gestation will have no discernible sequelae. The greatest risk for fetal varicella syndrome occurs in the first 20 weeks' gestation, with the highest risk (2%) between 13 and 20 weeks;¹⁷ a lower rate before 13 weeks (0.4%) may reflect underreporting or a higher rate of spontaneous abortion. Rare cases in the second half of pregnancy have been reported.^{18,19} A prospective study carried out in Germany and the UK between 1980 and 1993 identified 1373 women who had varicella and 366 who had zoster during the first 36 weeks' gestation. Nine cases of congenital varicella syndrome were reported overall, and all occurred after maternal varicella infection in the first 20 weeks of pregnancy. The highest risk occurred between 13 and 20 weeks' gestation, with seven cases noted in this subset. No cases of congenital varicella were noted following maternal herpes zoster during pregnancy. Herpes zoster in infancy was identified in 10 children whose mothers had varicella during pregnancy. Although 97 women who received varicella zoster immunoglobulin (VZIG) developed varicella, no cases of congenital varicella occurred in this group.¹⁷ Some believe that the failure to identify congenital varicella in late pregnancy reflects the limited statistical power of epidemiologic efforts, but nonetheless, late pregnancy is clearly a time of lower risk for the development of the classic stigmata of congenital disease.²⁰ It has been postulated that the severe segmental anomalies that can be seen in fetal varicella syndrome are the result of reactivation of primary varicella in the developing fetus at a time when the immune system is not sufficiently developed to modify the severity of infection.

Maternal herpes zoster does not appear to pose a significant risk to the fetus. No cases of congenital varicella occurred in a prospective study of 366 women who had zoster during pregnancy, and no serological evidence of transplacental transmission was noted.¹⁷ Approximately 18 cases of congenital anomalies occurring in association with maternal herpes zoster infection have been reported; however, it is not clear that these anomalies were a result of maternal zoster infection.²¹ A case of

TABLE 13.3 Features of fetal varicella syndrome

Characteristic organ system	Common (>50%)	Uncommon (<50%, >10%)	Rare (<10%)
Skin	Cicatricial lesions	Hydrocephalus and cortical atrophy vesicles	Cerebellar hypoplasia
Neurologic	Limb paresis	Seizures Horner syndrome Bulbar dysphagia Mental retardation Optic nerve atrophy Anal sphincter malfunction Microcephaly Phrenic nerve palsy Developmental delay and encephalomyelitis	Auditory nerve palsy Facial nerve palsy
Eye	Chorioretinitis	Anisocoria Nystagmus Microphthalmia Cataract	Corneal opacity Heterochromia
Skeletal	Hypoplasia of upper or lower extremities	Hypoplasia of fingers or toes Equinovarus or calcaneovalgus Hypoplasia of scapulae or clavicles Hypoplasia of ribs	Hypoplasia of mandible Scoliosis Lacunar skull
Gastrointestinal	Low birthweight		Gastroesophageal reflux Duodenal stenosis Dilated jejunum Small left colon Sigmoid atresia
Genitourinary			Absence of kidney Hydronephrosis Hydroureter Undescended testes Bladder abnormalities

cutaneous lesions and limb hypoplasia in a fetus whose mother developed disseminated herpes zoster at 12 weeks' gestation did appear consistent with fetal varicella syndrome, but localized maternal zoster has not been clearly implicated as a cause of fetal disease.²²

Diagnosis

The denuded or scarred areas seen with fetal varicella syndrome may be mistaken for aplasia cutis congenita or Bart syndrome. Other congenital viral infections should be considered in any infant presenting with microcephaly, ophthalmologic, or neurologic abnormalities.

Prenatal diagnosis of fetal varicella syndrome using viral or immunologic methods is unreliable.²³ IgM may be undetectable, even in infants with classic clinical findings. Infection before 18 weeks' gestation may lead to a suboptimal or altered immune response resulting from immaturity of the fetal immune system. Prenatal diagnosis of intrauterine exposure to varicella may be accomplished by means of cordocentesis, amniocentesis, and chorionic villus sampling.²³ IgM may be detected in cord blood as early as 19–22 weeks' gestation. Virus can be grown from amniotic fluid and fetal blood samples, and DNA probes can be utilized to evaluate placental tissue.^{24,25} However, transplacental transfer of virus can occur without any significant sequelae to the fetus, and the degree of fetal involvement cannot be determined by immunologic or viral evaluation. Thus, although the above-mentioned evaluations may be useful in diagnosing fetal varicella syndrome, they are neither

sensitive nor specific enough to accurately determine which fetuses will suffer untoward effects.

High-quality ultrasound at 20–22 weeks' gestation has been used as a means of surveying at-risk fetuses. Sonographic abnormalities include fetal hydrops, polyhydramnios, abnormal foci within the liver, microcephaly, and limb hypoplasia.²⁶ Unfortunately, some findings may not be apparent until later in pregnancy. A report of a fatal case of varicella embryopathy that used ultrasonography and MRI at 26 and 32 weeks' gestation found a high correlation between fetal imaging and subsequent pathologic findings, including limb involvement and even dermatologic features; however, MRI scanning was required to identify CNS abnormalities. The authors recommend combining prenatal ultrasonography with MRI in any woman noted to have varicella seroconversion during pregnancy.²⁷

Varicella virus is not usually isolated from live-born infants with congenital infection, and other findings must be used to confirm the diagnosis. Criteria useful in confirming the diagnosis include clinical, virologic, or serologic evidence of maternal varicella infection during pregnancy; erosions or scars in a dermatomal distribution; and immunologic evidence of varicella infection in the infant, including IgM antibody or persistence of IgG antibody beyond 1 year of life in the absence of clinical varicella infection. The development of herpes zoster in the first year of life without a prior history of varicella infection is also good evidence that the infant was exposed to varicella zoster during gestation. In rare instances, varicella virus particles have been detected by means of electron microscopy in skin samples obtained at or near birth.²⁴

Treatment

Prevention by eliminating natural infection during pregnancy is the best approach to this disease, and should be facilitated by the increasing use of the varicella vaccine in childhood. Ideally, pre-conception evaluation should identify at-risk women, who should then receive the varicella vaccine before conceiving. No fetal anomalies have been reported in infants born to pregnant women who have received the vaccine inadvertently. Nonetheless, the vaccine, which is a live attenuated virus, is contraindicated in pregnancy.

Therapeutic abortion is not automatically recommended to at-risk mothers as the risk of a fetal anomaly following exposure is so small.²⁸ At-risk mothers known to have recent exposure to varicella during the first 20 weeks of pregnancy should have varicella serologic evaluation. Latex agglutination (LA), immunofluorescent assays (IFA), fluorescent antibody-to-membrane antigen assays (FAMA), and enzyme-linked immunosorbent assays (ELISA) are sensitive and specific.²³ The LA test is also rapid and simple, making it quite useful in evaluating at-risk pregnant women.

Varicella zoster immunoglobulin post-exposure prophylaxis may be offered to varicella-susceptible pregnant women. It may be administered within 96 h of exposure, but is most efficacious within the first 48 h. It does not reliably prevent maternal illness, but does modify the severity of infection. It is unclear whether VZIG prevents fetal varicella syndrome or neonatal infection, but there were no cases of fetal infection in 97 pregnancies complicated by maternal exposure and treated with post-exposure VZIG prophylaxis.^{17,29} Because fetal varicella syndrome is so rare, larger studies would be required to confirm protection. Exposed pregnant women who are seropositive for VZV do not require VZIG.

Treatment with acyclovir should be considered in any pregnant women with varicella, particularly those in the third trimester, because of the risk of severe maternal disease, and to minimize the risk of neonatal disease in case delivery occurs during or soon after acute infection. The drug is usually well tolerated with little toxicity to the mother, but the risks and benefits to the mother and fetus have not yet been clearly delineated. The International Registry of Acyclovir Use During Pregnancy has followed at least 1246 fetal exposures to the drug, and no increased incidence of fetal abnormalities in exposed infants has been noted.³⁰ It has not been determined whether such treatment will eliminate the risk of varicella embryopathy or infantile zoster in exposed fetuses. Ophthalmologic and neurologic evaluation of the infant born to a mother with varicella during pregnancy is indicated, as is careful examination of the musculoskeletal, genitourinary, and gastrointestinal systems for underlying anomalies.

NEONATAL VARICELLA

Neonatal varicella may result if a mother develops chickenpox before or immediately after delivery. If maternal varicella occurs from 5 days before to 2 days after delivery, the in utero-inoculated fetus is at high risk for severe disseminated disease.

Cutaneous findings

The clinical course of neonatal varicella can be quite variable. Those who are more likely to develop severe illness generally develop skin lesions within 5–10 days after delivery. Some



Figure 13.9 Neonatal varicella. Generalized crusted papules. (Courtesy of Dr Gerald Goldberg.)

children will develop a few cutaneous lesions, but otherwise remain well. Lesions often appear initially as small pink to red macules that relatively rapidly become papular and subsequently develop a teardrop-shaped vesicle. Other patients initially develop crops of cutaneous lesions that may evolve into hemorrhagic and/or necrotic vesicles (Fig. 13.9).

Extracutaneous findings

Disseminated infection with widespread cutaneous and visceral involvement may develop and lead to severe morbidity. The mortality rate for neonatal varicella before the use of acyclovir has been estimated at 10–30%.^{28,29} Death from severe pneumonia and respiratory distress often occurs 4–6 days after onset of lesions. Hepatitis and encephalitis may also develop. A study from Thailand in 1999, evaluating 26 children with neonatal varicella, reported no mortality. Of the 26 children, 12 received intravenous acyclovir.³¹

Etiology and pathogenesis

Infants may develop lesions from 1 to 16 days after birth if the mother experiences active disease near the time of birth. The usual onset of rash is 9–15 days after onset of maternal rash. Administration of VZIG may prolong the incubation period to 28 days.¹⁴ In aggregate data from two studies, 23–62% of infants whose mothers developed varicella in the last 3 weeks of pregnancy developed neonatal varicella.¹⁷ The risk of severe neonatal varicella is related to the timing of maternal infection, presumably because of a critical period when transmission of virus to the infant occurs prior to the development and transplacental transfer of maternal antibodies, which modify expression of the infection in the neonate.

Diagnosis

Smears of vesicles using a Tzanck preparation will demonstrate multinucleate giant cells and margination of chromatin. VZV PCR evaluation is also helpful and is more specific for VZV; vesicular swabs, scrapings, biopsy tissue and CSF can be evaluated by PCR analysis. Direct fluorescent antibody (DFA) tests are less sensitive than PCR and occasionally false-positive in disorders such as incontinentia pigmenti and Langerhans' cell histiocytosis; therefore positive viral culture or PCR remain the best, most reliable means of diagnosis.³² A history of maternal varicella infection during pregnancy is also helpful but not necessary to confirm the diagnosis because infants may also contract the disease from siblings, care givers, and other close

contacts. The differential diagnosis of vesiculopustular lesions is discussed in [Chapter 10](#).

Treatment

Prevention is the best intervention. Delaying delivery until sufficient time has elapsed for transplacental transfer of maternal antibody is one approach; this generally occurs 5–7 days after the onset of maternal illness. Neonates born to mothers who have developed varicella from 5 days before to 2 days after delivery should receive VZIG intramuscularly as soon as possible after delivery.¹⁴ Direct contact between the infant and maternal skin lesions should be avoided, but breastfeeding is not prohibited if such contact can be avoided. Neonates who develop lesions or signs of infection should be treated with intravenous acyclovir, 20 mg/kg every 8 h for a minimum of 10 days. More prolonged therapy of 14–21 days may be necessary for disseminated or CNS infection.¹⁴ Aggressive supportive therapy is sometimes also required. The use of prophylactic acyclovir in high-risk infants has also been suggested by some authors.

It should be borne in mind that any infant born to a woman who has had varicella within 3 weeks of delivery may be infectious at birth or shortly thereafter. If onset of maternal infection is within 1–2 weeks of delivery, many experts recommend that the child be isolated (from at-risk hospital personnel and other babies) from birth. If onset of disease occurs in the mother within 1 week of delivery, or following the birth of the infant, the infant should be isolated 7 days after the onset of maternal disease.¹⁴

If a mother develops a varicella rash 3 or more days after delivery, the infant may contract varicella but this will more likely be via the respiratory route, which theoretically leads to a smaller systemic inoculum and less severe disease. However, serious illness has been reported in the first 4 weeks of life when infants contract disease from their mother or siblings during this period. Severe infantile disease may occasionally occur even in infants born to immune mothers.³³ If the mother is seronegative and the infant is exposed to an infectious sibling, many experts would recommend VZIG post-exposure prophylaxis for the infant. Post-exposure prophylaxis with acyclovir may be effective in older infants, but no data exist for its efficacy or safety in neonates. Although the mortality rate following non-congenital infantile varicella (0.008%) is higher than that in older children, it is still lower than the rate in immunocompromised individuals (7%) or following intrauterine exposure (10–30%).²⁶

Special concerns for the neonatal nursery and intensive care unit

Varicella exposure in the neonatal intensive care unit. Recommendations regarding prophylaxis after VZV exposure vary. The UK Advisory Group on Chickenpox recommends routine administration of VZIG to all neonates following exposure. If sensitive and rapid testing is available, exposed infants may be tested and the use of VZIG avoided for those with passive antibody to VZV. Others recommend concentrating prophylactic measures on those infants less than 30 weeks old and weighing less than 1 kg. The Report of the Committee on Infectious Diseases of the American Academy of Pediatrics recommends VZIG for all exposed, hospitalized premature infants who are less than 28 weeks' gestation, or who weigh 1 kg or less at birth. In addition, those exposed, hospitalized premature



Figure 13.10 Early varicella zoster in an infant whose mother contracted varicella during pregnancy.

infants of 28 weeks or more gestation, born to mothers who are seronegative or lack a history of varicella infection, should also be given VZIG.¹⁴

INFANTILE HERPES ZOSTER

Following primary infection, the varicella zoster virus persists in the sensory dorsal root ganglia and is kept in check by cell-mediated host immune mechanisms. Reactivation of the virus can occur and generally leads to localized involvement of skin and nerves in a dermatomal pattern corresponding to the ganglion in which reactivation took place. This disease, termed herpes zoster, has been recognized since antiquity. The term 'zoster' (*girdle* in Greek) refers to the tendency of the lesions to involve the trunk in a 'girdle-like' pattern. Infants may develop classic herpes zoster without prior evidence of primary varicella if exposed to varicella virus in utero. Neonatal herpes zoster has only rarely been reported. It is generally a benign disease without significant morbidity or sequelae for the infant unless the infant is immunocompromised.

Cutaneous findings

Affected infants usually have discrete lesions that involve predominantly the thoracic dermatomes. The lesions initially appear as a group of small pink to erythematous papules that subsequently vesiculate and crust ([Figs 13.10, 13.11](#)). Occasionally lesions become hemorrhagic and develop necrotic eschars. Scarring may occur in the involved area. Although the disease may disseminate, immunocompetent children usually have a benign course and an excellent outcome.

Diagnosis

The diagnosis is usually straightforward when the lesions assume a dermatomal distribution. A Tzanck preparation is the most rapid means to evaluate suspicious vesicular lesions. Zoster lesions may be initially mistaken for arthropod bites or impetigo. Herpes simplex infections may mimic herpes zoster but are usually more localized, with the potential to recur. Direct fluorescent antibody testing and PCR evaluation are also relatively rapid diagnostic techniques (see '[Infantile varicella](#)',



Figure 13.11 Infantile herpes zoster. Numerous erythematous vesicles concentrated in a dermatomal distribution. (Courtesy of Dr Angela Hernandez-Martin.)

below). Varicella virus can be isolated from vesicular lesions of herpes zoster.

Etiology and pathogenesis

Pediatric herpes zoster is more common in immunocompromised children, and in immunocompetent children within the first year of life who have been exposed to varicella in utero.¹⁸ The risk of infantile herpes zoster increases if exposure to varicella zoster virus occurs in the second half of pregnancy.¹⁷ Approximately 2% of fetuses exposed to VZV during the second half of pregnancy will develop herpes zoster during infancy.¹⁷

Treatment

Many infectious disease experts treat zoster in neonates with systemic acyclovir. Immunocompetent infants with zoster generally do well and do not require antiviral therapy. Patients who develop severe hemorrhagic disease, as well as those with disseminated lesions, are likely to benefit from systemic therapy. Supportive therapy in all cases should include good hygiene at the blister sites, compresses as needed, and treatment for secondary bacterial infection if indicated.

INFANTILE VARICELLA (CHICKENPOX)

Primary varicella (primary VZV, chickenpox) was a nearly universal childhood illness, until the widespread use of the VZV (Oka strain) vaccine. The two dose vaccine series is recommended for 1- and 4-year-old children. In those infants who do not have passive immunity from the mother, and as passive humoral immunity wanes, infants aged 1–12 months may be at risk for primary VZV. However, widespread use of the VZV vaccine in the older, eligible population offers protection to this group and led to an 89.7% decrease in infantile VZV (ages 0–12 months) from 1995 to 2008.³⁴

VZV is transmitted via respiratory droplets. Fever, headache, myalgias and arthralgias precede the earliest skin lesions, which develop 1–2 days after exposure. Lesions evolve quickly from a red papule to a small vesicle on a red base, classically described as a 'dewdrop on a rose petal'. The vesicles occur in crops and then crust, leading to the appearance of lesions in different stages (Fig. 13.12). Painful mucosal erosions may also develop. Skin lesions may heal with scarring. The disease spontaneously resolves in healthy children, but there is a risk of secondary bacterial infection. Infants with a compromised immune system, such as those with leukemia, lymphoma, HIV, or taking immunosuppressive medications, are at increased risk of complicated disease, which may also include thrombocytopenia and respiratory compromise.

In older infants (ages 12–23 months) who have received the VZV vaccine, post-vaccine vesicular eruptions may occur. PCR analysis has detected the vaccine strain VZV (Oka) in some of these lesions. Post-marketing surveillance data shows that the vaccine strain VZV (Oka) is most likely to be associated with the post-vaccine vesicular eruptions occurring between days 15 to 42 after the vaccination, whereas those occurring within 2 weeks or >42 days later are more likely secondary to wild-type VZV.³⁵ VZV infections acquired after 42 days, termed breakthrough varicella, are milder than the native disease, with fewer lesions (usually ≤50), more morbilliform appearance, lower fever and shorter duration. Post-vaccine herpes zoster (HZ) eruptions also occur. In contrast to wild-type HZ cases,

Oka-associated HZ cases showed a trend towards occurring in younger children (median age 2 years), near the site of vaccination, and with a shorter latency after vaccination.³⁵

Primary VZV can be diagnosed with history and physical examination. Adjunctive laboratory tests including Tzanck smear, PCR, direct fluorescence antibody (DFA), serologies and viral culture (described above) may be helpful if diagnosis is in doubt.

Treatment of primary VZV in healthy children is not recommended, as studies have not shown meaningful reduction in the development of new lesions or the total number of lesions with antiviral therapy (acyclovir).³⁶ In contrast, intravenous acyclovir should be started early (within 24–72 h of skin lesions) for immunocompromised children. In high-risk individuals with known exposure to VZV, varicella zoster immunoglobulin (VZIG) should be administered within 48 h of exposure, although it may be given up to 96 h. Valacyclovir, 20 mg/kg per day, given three times daily for 5 days, has been used by some experts for treatment of varicella in high-risk and immunocompetent patients. This drug is currently licensed for children 2 years of age or older.

According to guidelines from the American Academy of Pediatrics, non-immunized infants with VZV must be excluded from childcare settings until all lesions are crusted over and those previously immunized may return when no new lesions have developed in 24 h.¹⁴ Infants with HZ may return if lesions can be adequately covered or when all lesions are crusted.¹⁴

Cytomegalovirus

Cytomegalovirus (CMV), one of the most common viral infections of the newborn, is acquired congenitally, perinatally, or postnatally. CMV, a member of the herpes virus family, is a double-stranded DNA virus. It represents the most frequently diagnosed congenital infection, occurring in 1–2% of all births.³⁷

Cutaneous findings

The principal cutaneous manifestations of CMV infection are similar to those of congenital rubella syndrome and consist of skin lesions of extramedullary hematopoiesis ('blueberry muffin' spots) and petechiae secondary to thrombocytopenia, which resolve during the first weeks of life.

Extracutaneous findings

Other manifestations of congenital CMV infection syndrome include intrauterine growth retardation, microcephaly with chorioretinitis, hepatosplenomegaly, and pneumonitis.

Etiology and pathogenesis

Congenital infection occurs most often following reactivation of latent maternal infection during pregnancy, resulting in viremia and/or transplacental transmission of lymphocyte-associated virus to the fetus. The vast majority of infected infants born to immune mothers with reactivation of CMV are normal, and have no stigmata of congenital infection. However, seronegative mothers may acquire a primary CMV infection during pregnancy, leading to a far greater incidence of symptomatic disease in the neonate. The severity of infection depends on the trimester in which fetal infection has occurred, with infections early in gestation leading to more pronounced clinical findings and a poorer prognosis than those acquired during



Figure 13.12 Primary varicella in an infant. Erythematous macules, papules and vesicles.

the third trimester. Infection may also occur at the time of delivery following exposure to infectious secretions during the process of vaginal birth. The infection is acquired perinatally in 40% of infants born to culture-positive mothers. Postnatal transmission has also been well-documented in breast-fed infants following the ingestion of culture-positive breast-milk.

Diagnosis

The virus can be isolated from urine, pharynx, saliva, peripheral blood leukocytes, and a host of other tissues. Culture is the most widely available method of diagnosis. Quantitative PCR techniques can be used in assessing white blood cells, CSF, and other tissues. Infants with congenital infection are, by definition, culture positive at the time of birth. For a diagnosis of congenital infection, cultures should be obtained within the first 2 weeks of life. If cultures are positive in the infant beyond 1–2 weeks of age, it is not possible to differentiate between congenital and perinatal CMV infection. This distinction is often critical, however, as the prognosis for perinatal CMV is uniformly good, whereas that of congenital CMV is not. Skin biopsies do not usually reveal evidence of active CMV infection, although specimens from liver, lung, or kidney will show clear evidence of CMV inclusions in infected parenchymal tissues. A spun sample of urine may demonstrate viral inclusions in tubular epithelial cells in up to 50% of culture-positive samples, and may demonstrate CMV by electron microscopy in up to 93% of culture-positive urine samples.³⁸ Serologic studies can also be used to make a diagnosis of congenital/perinatal CMV infection, either by demonstrating specific CMV-IgM antibody produced by the neonate or by documenting a persistent, increasing titer of IgG antibody during the first 4–6 months of life. Although the presence of specific CMV-IgM in cord blood will verify congenital infection, the sensitivity of this test as currently performed in reference laboratories may be less than 50%. PCR testing for CMV-DNA is accepted as a very sensitive diagnostic technique for plasma and certain tissue fluids in immunocompromised hosts, and is a highly sensitive test in the newborn.³⁷

Treatment

Vaccines have been in development for several years but have not demonstrated sufficiently adequate protection from CMV infection to justify their extensive use. Currently, treatment of CMV infections is primarily accomplished with parenteral ganciclovir or oral valganciclovir, its oral prodrug; both are nucleoside analogs with potent activity against most strains of CMV.³⁹ The drug is associated with significant bone marrow toxicity. Clinical trials of intravenous ganciclovir for congenital CMV demonstrated a significant reduction in hearing loss at 6 months in infants with CNS (central nervous system) manifestations of congenital infection.⁴⁰ Unfortunately, congenital CMV infections cannot be cured but only suppressed during the period of antiviral administration. Limited data exist on the use of oral ganciclovir and valganciclovir in the neonate.⁴¹

Rubella

The association of maternal rubella infection with congenital disease of the newborn was first recognized in 1941. Extensive investigations have resulted in delineation of the congenital rubella infection syndrome, typified by a small-for-gestational age infant with microcephaly, deafness, cataracts, heart defects,

chorioretinitis, hepatosplenomegaly, and a papular rash on the face, trunk, and extremities.

Cutaneous findings

The rash can be mild or extensive, and is a manifestation of intradermal sites of extramedullary hematopoiesis (EMH). It often becomes hemorrhagic secondary to thrombocytopenia present at birth in these infants. The initial ‘cranberry muffin’ character of these 2–20 mm raised, erythematous, soft, spongy lesions changes to the more characteristic appearance of ‘blueberry muffin’ spots following intralesional hemorrhage. Petechiae may also be present in addition to the lesions of EMH. The lesions of EMH are not specific for rubella infection, and may also occur with congenital cytomegalovirus and toxoplasma infections. Petechial and purpuric lesions are evident in up to 60% of infants with congenital rubella.

Extracutaneous findings

Associated clinical findings, beyond those listed previously, include congenital heart disease (patent ductus arteriosus, pulmonary stenosis, aortic stenosis), cataracts, and pneumonia, which may actually develop and progress after birth. Psychomotor retardation and deafness occur in up to 50% of infants with documented congenital rubella syndrome.⁴²

Etiology and pathogenesis

Maternal infection gives rise to viremia, which is transmitted to the fetus, affecting rapidly dividing fetal tissues most prominently during the first 12 weeks’ gestation. This single-stranded RNA virus usually causes a noncytolytic infection of cells, leading to cell dysfunction and defects in organogenesis. Although fetal infection may occur at any time during gestation, visible consequences of infection are most common following first-trimester infection, rare with a second-trimester infection, and virtually nonexistent following infection late in pregnancy.⁴³

Diagnosis

Viral culture of the nasopharynx is the definitive method of confirming the diagnosis of rubella infection (Table 13.1), as virus shedding continues for several weeks to months after birth. Detection of rubella-specific IgM is helpful, but both false-positive and -negative results can occur. Assessing the maternal serologic status can be helpful, but many ‘prenatal’ serologies are actually performed at the end of the first trimester and therefore do not truly represent the mother’s immune status before pregnancy and cannot rule out infection at week 12 of gestation. If the infant is believed to have been infected, acute (cord blood) and convalescent (obtained at 4–6 months of age) blood samples should be obtained to determine antibody titers for rubella. These titers are diagnostic, as virtually all maternal transplacental antibodies will have disappeared from the infant by 6 months of age. Evaluation of the cutaneous lesions will lead only to the nonspecific diagnosis of EMH.

Prevention and treatment

No specific antiviral therapy exists for rubella virus. In the USA, universal immunization of children is specifically designed to prevent congenital rubella infection. Prenatal screening of women during early pregnancy should detect susceptible individuals, and immunization immediately following the pregnancy is indicated.

Acquired immunodeficiency syndrome

Acquired immunodeficiency syndrome (AIDS) is a multisystem disorder characterized by T-lymphocyte depletion and recurrent opportunistic infections. It results from infection with the human immunodeficiency virus (HIV), an RNA retrovirus that infects CD4 T lymphocytes, as well as other immune cells. Transmission can occur in utero, perinatally, or via breast-milk. It can also be transmitted via sexual contact, percutaneous blood exposure, mucous membrane exposure to contaminated blood, and via blood transfusion. Characteristics of the infection include a variable latency period and an extremely high mortality rate if untreated. Perinatal transmission from infected mothers is the most common cause of childhood infection.⁴⁴ The number of pediatric cases decreased by 90% in 2002 compared with 1992, mainly because of a decrease in perinatal transmission due to screening for HIV during pregnancy, with antiretroviral treatment of the mother at the end of pregnancy and treatment of the newborn for the first 6 weeks of life.^{14,44} Most infected infants are asymptomatic in the first few months, but severe disease can occur within this time frame. Cutaneous abnormalities are among the earliest findings, and may be infectious, inflammatory, or neoplastic in nature. Failure to thrive, recurrent infections, and pulmonary disease (relating to *Pneumocystis jiroveci* or lymphoid interstitial pneumonia) are common findings in infants. These children are also at risk for gastrointestinal disorders, including malabsorption, hepatosplenomegaly, and CMV-mediated organ involvement such as hepatitis and marrow failure.

Cutaneous findings

Cutaneous and mucous membrane disease is very common in infants with symptomatic HIV infection. Frequently, the first indication that an infant is infected is the development of a severe or recurrent bacterial or fungal infection. In other instances, widespread and protracted seborrheic dermatitis may be the first clue to the patient's underlying immunodeficiency. Cutaneous infections that are extensive, progressive, or difficult to treat, should raise suspicion for HIV infection. The type of cutaneous involvement that occurs with disease is generally related to the degree of immunosuppression.

Infectious skin disorders. Mucocutaneous candidiasis is the most common dermatologic manifestation of pediatric HIV infection and occurs in the overwhelming majority of symptomatic children.⁴⁵ The disease is more severe and chronic than in the immunocompetent host and frequently persists beyond the first 6 months of life. White, cheesy patches or plaques overlying an erythematous base are found on the buccal mucosa, tongue, and palate. The lesions are friable and in severe cases, may extend to involve the esophagus. The diaper area is commonly involved, with a beefy-red erythema involving the convex surfaces and creases, along with satellite papules or pustules. There may be angular cheilitis and extensive, generalized cutaneous involvement. Severe dermatophyte infections of the nails, hair, and skin may develop, and other unusual fungi, such as *Cryptococcus* spp. and *Aspergillus* spp. may cause systemic as well as cutaneous disease.⁴⁶

Bacterial infections of the skin may take the form of severe and recurrent staphylococcal impetigo, folliculitis, cellulitis, or abscesses. Other more unusual pathogens may be noted,

particularly when the patient is severely immunosuppressed. Although polymorphonuclear (PMN) function against bacteria is not altered, T/B-cell cooperation leading to opsonizing antibacterial function may be severely affected.

Viral infections are also atypical in course and lesion morphology. The lesions of varicella zoster infection may become chronic, hemorrhagic, ulcerating, and/or hyperkeratotic.⁴⁷ Herpes zoster occurs earlier and more frequently in HIV-infected children. Herpes simplex infections may also be severe, prolonged, and/or recurrent. Molluscum contagiosum and papilloma virus infections are more frequent and may be relatively refractory to therapy.

Scabies can occur in early infancy and may present in a severe crusted form, often referred to as Norwegian scabies. Such cases are highly infectious because the affected infant usually possesses numerous generalized crusted papules that harbor large numbers of organisms.

Neoplastic skin disease. Cancer is the presenting sign for AIDS in only 2% of children, compared with 15% of adults.⁴⁸ Kaposi sarcoma (KS) is significantly less common in childhood than in adult AIDS. However, a report from Zambia noted a significant increase in the incidence of pediatric KS since 1987.⁴⁹

Kaposi sarcoma has been described in a 6-day-old infant, but is rare in the neonatal period.⁵⁰ Non-Hodgkin lymphomas, which are sometimes limited to the CNS, occur with increased frequency in children with AIDS, as do leiomyomas and leiomyosarcomas.⁵¹

Inflammatory skin disease. Confluent beefy erythema with superimposed greasy thin scale first noted on the scalp and face is characteristic of seborrheic dermatitis in children with AIDS. It spreads to involve the axillae and diaper area, and occasionally may progress to a severe, generalized erythroderma. Atopic dermatitis and psoriasis can also occur in HIV-infected patients, but are not commonly diagnosed in the neonatal period. Drug eruptions, particularly from trimethoprim-sulfamethoxazole, are more frequent in children with AIDS.⁵² The rash usually develops within 7–10 days after the start of therapy and is a pink, papular or morbilliform eruption. Evolution to TEN (toxic epidermal necrolysis) may occur, but most eruptions resolve following discontinuation of the offending agent.

Extracutaneous manifestations

An HIV-related embryopathy described in 1986, and characterized by microcephaly and dysmorphic facial features, has not been substantiated. The papular exanthem/enanthem that develops shortly after HIV infection in adults has not been noted in perinatally acquired disease.⁵³

Clinical conditions that should raise suspicion for HIV infection include failure to thrive, recurrent severe bacterial or opportunistic infections, hepatitis, lymphoid interstitial pneumonia, parotitis, lymphadenopathy, and hepatosplenomegaly. *Pneumocystis jiroveci* pneumonia is the most common serious opportunistic infection in HIV-infected children and usually develops between 3 and 6 months of age; however, infection can occur in infants as young as 4–6 weeks. Patients may also develop severe wasting, encephalopathy, developmental delay, nephropathy, cardiomyopathy, and diarrhea.

Etiology and pathogenesis

HIV is a human retrovirus containing RNA. Two forms exist: HIV-1, most prevalent in the USA, and HIV-2, a related virus more commonly seen in West Africa. The virus has a predilection for CD4 lymphocytes, glial cells, macrophages and monocytes, and infection generally leads to significant impairment in cell-mediated immunity.

HIV is transmitted by contaminated blood, semen, human milk, and cervical secretions. The virus has also been isolated from saliva, tears, urine, cerebrospinal fluid, and pleural fluid, but these have not been shown to routinely transmit infection.

Many sources have documented that perinatal transmission of HIV accounts for the overwhelming majority of pediatric cases in the USA.⁴⁴ Infection may be transmitted to the infant in utero, at the time of delivery, or through breast-feeding. The risk of infection for an infant whose mother did not receive interventions to prevent transmission is approximately 13–39%.¹⁴ The risk of intrapartum transmission is higher than for intrauterine spread. In areas with high rates of breast-feeding, one-third to half of maternal transmissions occur through breast-feeding. It is thought that the majority of infections are transmitted close to or at the time of delivery. Routine prenatal screening for HIV infection and treatment of infected women and their infants with antiviral agents such as zidovudine, and other antiretrovirals, are recommended. If an infected mother is compliant with antiretroviral medications and her viral load is <1.00 copies/mL, her risk of vertical HIV transmission decreases to 1%. Cesarean section delivery decreases the risk of HIV transmission to the fetus by approximately 50%, presumably because the infant has a reduced exposure to maternal blood and cervical secretions.⁵⁴ The combined use of maternal antiviral therapy and cesarean section delivery can theoretically reduce the risk of transmission to approximately 0.5%.

The incubation period for HIV infection is quite variable. Infants are generally asymptomatic during the first few months of life. The median age of onset for perinatally acquired untreated disease is 12–18 months. Conversely, severe illness can develop in the first few months of life. Approximately 10–15% of children will die before 4 years of age.¹⁴

Diagnosis

Diagnosis during infancy requires the detection of the virus or viral nucleic acid, as almost all infants born to HIV-seropositive mothers will have transplacentally acquired antibodies, which may persist for up to 18 months. It is therefore necessary to document infection using other methods in the newborn and young infant. A positive viral culture is diagnostic; however, only 25–50% of infected children will be identified at birth by means of culture. In addition, viral culture is expensive, not widely available, and requires up to a month for the results. PCR evaluation is a very sensitive and widely available method for the detection of HIV infection in the neonatal period, and is currently recommended. HIV DNA PCR is the preferred test to diagnose HIV-1 infection in infants and children younger than 18 months of age. It is highly sensitive and specific.

Approximately 30% of HIV-infected infants will have positive PCR studies within the first 48 h of life, and 93% will be positive by 2 weeks of age.⁵⁵ If initial evaluation within the first 48 h is negative, repeat tests should be performed at 1–3 months, and then again at 4–6 months if necessary.⁵⁵

Laboratory findings suspicious for HIV infection include a decreased ratio of helper to suppressor T cells, and hypergammaglobulinemia. One study suggested that elevated IgG levels and oral candidiasis in children less than 15 months of age had a high (98%) specificity for the diagnosis, but low sensitivity (37%).⁵⁵ Lymphopenia is not usually seen in infants and children. Microcytic, hypochromic anemia is common, and thrombocytopenia may also be present. Because cutaneous disease in HIV-infected patients often presents in an atypical fashion, culture and biopsy of any suspicious lesion should be obtained if the diagnosis is in doubt.

Treatment

Treatment options and recommendations change with time. CDC guidelines are continuously updated, are available on the CDC website, and represent the most current consensus on treatment (see: www.aidsinfo.nih.gov for updates regarding interventions). Zidovudine therapy of the HIV-infected pregnant woman and the newborn infant can significantly decrease perinatal transmission, as can caesarean section delivery (see above). Oral administration of zidovudine to the infant for 6 weeks further reduces the risk of perinatal transmission. Most infected pregnant women are on combination antiretroviral therapy. Short-term adverse effects of the drug include anemia, neutropenia, and hepatitis. No long-term adverse side-effects have been noted.⁵⁶ Breast-feeding by HIV-infected women is not recommended in areas where safe alternative options are available.

Infected infants should be referred to an HIV specialist. Chemoprophylaxis with TMP/SMX (trimethoprim-sulfamethoxazole) reduces the risk of infection with *Pneumocystis jiroveci* and may reduce the incidence of cutaneous bacterial infections. Cutaneous infections with fungi, bacteria, and viruses should be treated as appropriate for each disease. Candidiasis usually requires systemic therapy, and fluconazole has proved particularly useful for this purpose. Acyclovir therapy is appropriate for the treatment of herpes simplex and zoster infections, but chronic use may lead to acyclovir resistance, which is more common in the AIDS population. Foscarnet and ganciclovir have both proved to be efficacious antiviral agents in immunocompromised patients.

Human parvovirus B19 infections

Parvovirus B19 infection is classically associated with a benign viral exanthem of childhood (erythema infectiosum) consisting of a distinctive ‘slapped cheek’ appearance, followed by a reticulate, lacy truncal eruption. The virus can also less commonly manifest other findings in children and adults (Table 13.4), as well as in the developing fetus and infant.⁵⁷ The range of clinical manifestations caused by parvovirus B19 is diverse. Red blood progenitor cells are particularly susceptible to the virus, but it can also affect skin, liver, and myocardial cells. Although the majority of healthy individuals who are infected have few or no symptoms, the fetus is at particular risk for significant morbidity. Infection during pregnancy has been associated with an increased risk of miscarriage, fetal hydrops, intrauterine growth retardation, and isolated pleural and pericardial effusions.⁵⁸ The risk of fetal death is approximately 1–9%, with the greatest risk occurring during the first half of pregnancy.⁹ Recommendations for management of exposed pregnant women are summarized in Box 13.1. Symptomatic neonatal disease is rare and

TABLE 13.4 Manifestations of human parvovirus B19 infection

Host	Findings
Immunocompetent children	Erythema infectiosum, papular purpuric gloves and socks syndrome (adolescents)
Immunocompetent adults	Transient arthritis
Individuals with increased hemolysis, e.g., sickle cell disease	Transient aplastic crisis
Immunodeficient patients	Chronic anemia
Fetus (first 20 weeks' gestation)	Hydrops fetalis; pleural, pericardial, or peritoneal effusions; anemia
Neonate	Persistent anemia, red cell aplasia; blueberry muffin lesions (rare); myocarditis (rare)
Infant (1–24 months)	Acral papules and purpura; myocarditis (rare)

BOX 13.1 RECOMMENDATIONS FOR PREGNANT WOMEN EXPOSED TO PARVOVIRUS B19*

- Obtain titers; if IgG positive, check for IgM; if IgM negative, patient is immune with no risk
- If titers are negative, recheck in 2 months; if IgM then positive offer serial ultrasound follow-up

*Highest risk present in first 20 weeks of pregnancy.

usually consists of persistent anemia following congenital infection.⁵⁹

FETAL, CONGENITAL, AND NEONATAL DISEASE**Cutaneous findings**

The most common findings in affected abortuses are pallor, maceration, and subcutaneous edema, all consistent with the diagnosis of hydrops. Blueberry muffin lesions showing extramedullary hematopoiesis have also been reported.

Extracutaneous findings

Increased fluid may develop in the pericardial, peritoneal and pleural cavities. The exact risk of congenital anomalies following B19 infection is controversial, but is thought to be extremely low. Bilateral cleft lip and palate, micrognathia, subcutaneous hemorrhage, and congestion of internal organs have been found in fetuses in association with characteristic nuclear inclusions within erythroid precursor cells, endothelial, and smooth muscle cells.⁶⁰ Three live-born infants with severe neurologic defects whose mothers had serologically documented parvovirus infection during pregnancy have also been described.⁶¹ Significant ocular abnormalities involving the globe, retina, and cornea have been reported in one case.⁶² Large prospective studies have failed to note any significant risk of congenital abnormalities following maternal parvovirus infection.⁶³ Current consensus is that the risk of congenital infection from parvovirus is less than 1% and is not yet clearly determined.⁶⁴

Most cases of documented neonatal infection consist of persistent anemia following congenital infection.¹⁴ Isolated

congenital red cell aplasia, which may mimic Diamond–Blackfan anemia, may be caused by parvovirus B19 infection.⁶⁴ Relapsing erythroid hypoplasia in a 2-month-old infant has also been attributed to parvovirus infection. Multisystem disease in an infant who presented at birth with petechiae and thrombocytopenia and developed edema, cardiomegaly, bradycardia, and hypotension on day 2, has also been reported.⁶⁵ True neonatal disease is thought to be rare, but it is possible that it may be unrecognized and underreported. Unfortunately, technical problems in identifying neonatal infection make it difficult to ascertain the true incidence (see below).

Etiology and pathogenesis

Parvovirus is one of the smallest known DNA viruses to infect humans. It is a global pathogen with increased prevalence in the late winter and early spring in temperate climates. Periodic epidemics occur. The most common mode of transmission is person-to-person contact via respiratory secretions. The incubation period is 4–14 days, but can be as long as 21 days.⁶³ Parvovirus B19 can also be transmitted vertically from mother to fetus, and during transfusion with contaminated blood products.¹⁴ Since 2002, quantitative DNA measurement has been used to screen plasma products and thus reduce the risk of transmission through blood products.

Infection is rare in the first year of life, and the highest rate of infection occurs among children of school age. The prevalence of IgG antibodies in pregnant women is approximately 65%.⁵⁷ Secondary attack rates are highest with household contact. Pregnant women with a child aged 5–7 years in the household appear to have a higher risk of becoming infected than do those with children under 2 years of age. Of particular concern is the risk to seronegative women in daycare and school settings, because infection in the first 20 weeks' gestation can lead to increased fetal wastage and fetal hydrops. The greatest risk occurs during epidemics, and nursery school teachers appear to have a threefold increased risk of acute infection compared to other pregnant women.⁵⁷ Nonetheless, routine exclusion of pregnant women from the workplace is not recommended, as risk of infection from other contacts is also likely during epidemics.

Parvovirus B19 propagates in human erythroid cells. In normal hosts, the cytotoxic effect of the virus leads to cessation of red blood cell production for approximately 4–8 days, creating a significant stress in patients with a rapidly expanding red cell mass (e.g., second-trimester fetus), or decreased red cell survival (e.g., underlying hemolytic anemia). The cellular receptor for parvovirus B19 (globoside or blood group P antigen) is located predominantly on the surface of erythroid precursor cells, thus explaining the virus's affinity for this cell line. It is also present on myocardial cells, megakaryocytes, and endothelial cells, which may explain the thrombocytopenia, vasculitis, and myocarditis that are occasionally noted in affected fetuses and individuals. Immunocompromised hosts, presumably including fetuses, may have persistent viral infection and resultant chronic anemia.

The pathogenesis of hydrops secondary to parvovirus may be multifactorial. Severe anemia is almost always present and may lead to hypoxic injury and high output cardiac failure. Ascites, effusions, and skin edema may result. Myocarditis and diminished fetal cardiac output have also been noted in some cases, and may contribute to hydrops.

The exact risk to any pregnant woman (and her fetus) following exposure is not precisely known, although there appears to be a risk only if infection develops within the first 20 weeks' gestation. Various studies have estimated the risk of adverse fetal outcome following maternal infection to be from 1% to 9%, with greatest risk during the first half of pregnancy.⁵⁷ Prospective studies have shown an excess rate of fetal loss of 9%, confined to exposure during the first 20 weeks' gestation, and an incidence of fetal hydrops of 2.9% with maternal infection between 11 and 18 weeks' gestation.^{63,66} No significant risk for congenital anomalies has been noted. Spontaneous resolution of hydrops has been documented and complicates the issue of when and if intrauterine transfusion should be carried out (see 'Treatment', below).

Diagnosis

The diagnosis of acute parvovirus infection in pregnant women using IgM antibodies or IgG seroconversion is straightforward. Using radioimmunoassay or ELISA, over 90% of cases can be documented at the time of rash.¹⁴ The presence of IgM indicates that infection probably occurred within the previous 2–4 months. IgG levels are helpful to determine past exposure, and hence immunity, but are not helpful in detecting acute infection, as more than 50% of adults are seropositive. Fetuses, neonates, and immunocompromised patients may not mount an appropriate immune response following infection, and other methods may be required to document infection in these patients.

Parvovirus cannot be propagated in traditional cell culture. Virus may be identified using DNA hybridization techniques and PCR assays for B19.⁶⁰ PCR is the optimal test for diagnosing chronic infection in immunocompromised patients, and may persist for up to 9 months in immunocompromised patients.

Routine histopathologic evaluation may reveal the presence of characteristic intranuclear inclusions in nucleated erythroid cells in placental or fetal tissue. Immunohistochemistry may detect viral antigen by staining techniques. Electron microscopy has been used to detect virus particles in serum, and prenatally in amniotic fluid, fetal blood, and ascitic fluid, as well as in postmortem tissue.⁵⁸

Serologic evidence of infection in infants may be re-evaluated at 1 year of age, at which time maternal antibody should have disappeared and immunoglobulin detection will indicate true fetal or neonatal infection. Viral studies may fail to reveal acute infection if carried out subsequent to resolution of the infection. Viremia persists only 2–4 days in the immunocompetent host, and is generally absent by the time the classic rash develops.

Differential diagnosis

Nonimmune fetal hydrops can result from a number of diverse etiologies. It has been associated with many cardiac, infectious, hematologic, and genetic abnormalities, including anemias of diverse origins, CMV, toxoplasmosis, and syphilis.

Treatment

Management of the exposed pregnant woman. Serologic evaluation should be offered; if the woman has high IgG titers to parvovirus B19 and lacks IgM, she is immune and not at risk. If she is seronegative, titers should be rechecked in 2 weeks for the presence of specific IgM. If evidence of acute infection exists, serial ultrasonographic evaluation is suggested.^{67,68} α -Fetoprotein levels have also been used as a screening tool.^{67,68}

The risk of adverse outcome is minimal if infection occurs after 20 weeks' gestation, and is low even if the mother becomes infected in the first two trimesters.

Management of fetal hydrops. Fetal intrauterine digitalization and transfusion may be useful if significant fetal hydrops is observed. Although studies have shown reduced mortality with transfusion, its use is controversial because cases with spontaneous resolution of intrauterine hydrops can occur, and the procedure poses some risk to the fetus.

Congenital and neonatal infection. Neonates with congenital infection attributed to parvovirus may respond to intravenous immunoglobulin therapy. Supportive care, including transfusion, may be required. Immunosuppressed patients may benefit from IVIG therapy.

Parvovirus infection in infants and toddlers. Parvovirus in the older infant may present with the typical slapped cheek appearance and lacy peripheral eruption observed in school-age children, or may have less characteristic features. A juvenile variant of the papular purpuric gloves and socks syndrome (more typical of adolescents and young adults) has been described, in which infants develop erythematous and purpuric papules on the hands and feet lasting an average of 4–6 weeks. However, this presentation in infants has also been associated with other infections (EBV, CMV) and is not specific for parvovirus B19.⁶⁹ Recently, in India, human parvovirus B19 IgM antibodies were detected in 15 out of 24 patients who had fever and generalized erythroderma, which resolved after 7–10 days with desquamation.⁷⁰ Most of these patients were less than 1 year of age.

Parvovirus has also been associated with acute myocarditis in infants, and a prospective postmortem study of infants who succumbed to sudden infant death syndrome (SIDS) detected parvovirus B19 in cardiac tissue from 7 (11.2%) cases of SIDS.^{71,72}

Prophylaxis. A candidate recombinant vaccine composed of capsid proteins is in development and appears to be immunogenic, but a recent phase I/II trial was halted due to cutaneous reactions.^{73,74}

Enterovirus

The enteroviruses are a group of common, single-stranded RNA viruses that include the polioviruses, coxsackie viruses A and B, and echoviruses. Enteroviral infection in the neonate occurs most frequently during summer and early fall. Neonatal enterovirus infection can be severe, and the closely related parechovirus, a member of the same viral family (Picornaviridae), results in equally devastating disease. Neonatal enterovirus and parechovirus infections cannot be distinguished clinically.⁷⁵

Cutaneous findings

Perinatal disease occurs within the first few weeks of life and results in the nonspecific clinical symptoms of sepsis (fever, irritability, poor feeding), accompanied by skin findings in approximately one- to two-thirds of infants.^{76,77} The rash is most often maculopapular (morbilliform), macular, or petechial (Fig. 13.13). The vesicopustular lesions that occur on intact skin (lesions analogous to those seen in hand, foot, and

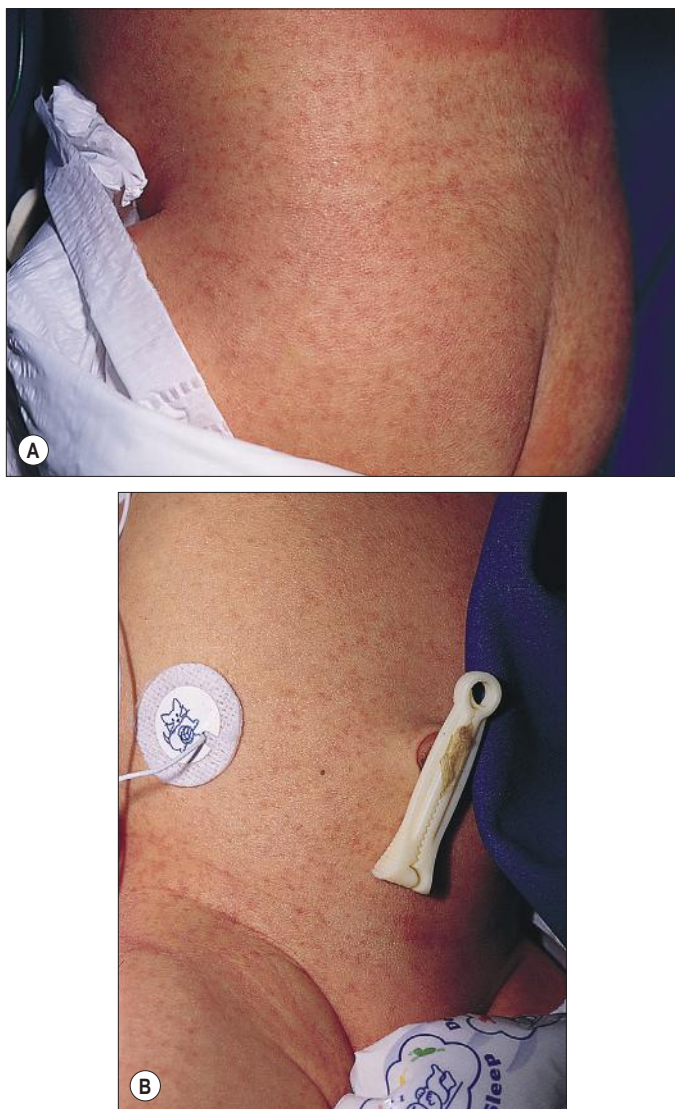


Figure 13.13 Generalized erythematous papular eruption associated with enterovirus infection.

mouth disease) develop secondary to viremia, not from local inoculation as is seen in HSV infections. The pharynx is often erythematous, but usually without lesions. However, ulcers consistent with herpangina may appear on the soft palate. These early lesions may be indistinguishable from those of HSV infection. With progression of the infection, oral lesions remain circular (2–4 mm in diameter), confined to the soft palate, and exhibit a ‘punched-out’ appearance surrounded by a rim of erythema. Unlike those of HSV, they do not continue to enlarge or involve the hard palate, buccal mucosa, or gingival sulci.

Extracutaneous findings

Systemic manifestations of infection may be mild or severe. Disseminated infection involving the lungs, liver, and CNS (in addition to the upper respiratory tract and skin) occurs more often in the premature than in the full-term infant. The amount of transplacental antibody present is likely to affect the severity of the infection; therefore the most overwhelming infections occur in premature infants who lack significant

amounts of specific maternal antibody for the infecting type of enterovirus.

In utero disease may occur rarely, with insufficient numbers of cases reported to consider a ‘congenital infection syndrome’. Findings in the neonate appear to result from residual damage to the heart, gastrointestinal tract, urogenital tract, muscle, or cutaneous tissue, rather than ongoing infection or reactivation of latent virus, with an apparent high intrauterine mortality rate.⁷⁸

Etiology and pathogenesis

Estimated rates of neonatal infection are between 2 and 38 cases per 1000 births.^{76,79} Modes of transmission to the infant are similar to those for HSV. Acquisition from maternal sources at the time of delivery occurs in the majority of neonatal infections, with congenital infection being reported only rarely.⁸⁰ Postnatal infection from sources other than the mother is also very common, leading to illness and frequent hospitalization of symptomatic infants during the first few months of life.

Diagnosis

Definitive diagnosis of enteroviral infection is most often achieved by PCR or viral culture of the pharynx or stool (Table 13.1). During acute infection, cultures of the pharynx are the most likely to yield the pathogen, whereas intestinal excretion of virus from gut-associated lymphoid tissue increases following clinical recovery. Fecal shedding of virus may continue for up to 6 weeks after acute infection, despite the presence of neutralizing antibody in serum. The PCR technique has been exceptionally useful in the diagnosis of enteroviral meningitis, and may be performed on the CSF of an infant whose rash is suspected to be enteroviral in origin.^{76,81} PCR of material from the pharynx, stool, or lesions has not been systematically evaluated. Histologic examination of the morbilliform skin eruptions does not yield specific cytologic information on the viral etiology of the rash. Serologies are not usually helpful, as no class-specific antibody response occurs with enteroviral infections, and at least 72 serotypes of enterovirus have been identified to date.

Treatment

Traditionally, only supportive care has been given; however, some experts recommend the administration of intravenous immunoglobulin to infants with overwhelming systemic infection.⁸² Specific antiviral therapy with a novel anti-picornavirus agent, pleconaril, is currently being evaluated in a double-blind, placebo-controlled trial in newborn infants with disseminated infection and has the potential to offer effective therapy for serious enteroviral infections.⁷⁶

INFANTILE ENTEROVIRAL DISEASE

Enteroviral infections in older infants commonly manifest as hand, foot, and mouth disease (HFMD), but severe illness such as myocarditis, polio, meningitis, and encephalitis can also develop, which may result in long-term sequelae.

HAND, FOOT, AND MOUTH DISEASE

Classic HFMD presents with fever, characteristic round to oval small vesicles on the palms and soles, and small vesicles and

erosions on the oropharyngeal mucosae and tongue. In some cases, the cutaneous lesions also involve the dorsal hands, knees, buttocks, thighs and genitalia or evolve into a diffuse vesicular eruption (Fig. 13.14). The oral enanthem is often painful and places the child at risk for decreased oral intake and dehydration. Weeks after infection, nail changes such as transverse ridging (Beau's lines) or onychomadesis may be noted (Fig. 13.15).

Several enteroviruses cause HFMD, including coxsackieviruses A5, A7, A9, A10, A16, B1, B2, B3, B5, echovirus 4 and enterovirus 71.⁸³ Most North American HFMD is due to coxsackievirus A16, however, more severe cutaneous disease linked to coxsackievirus A6 has been recognized in the USA since 2011 and CDC surveillance indicates a higher than expected rate of coxsackievirus A6 HFMD in children <2 years of age.⁸⁴ Previously associated with international outbreaks in Finland, Taiwan, Japan, and Singapore, the coxsackievirus A6 exanthem appears to be more extensive, and may have unusual features such as erosions, an eczema herpeticum-like appearance, or a petechial or hemorrhagic appearance.⁸⁵

Human papilloma virus infections

Infection with the human papilloma virus (HPV) can lead to cutaneous infections that commonly manifest as warts on the skin or mucous membranes. Lesions may be spread by direct sexual or nonsexual contact. Mother to infant transmission can be transplacental or via exposure to cervical or genital lesions. Autoinoculation or transmission via sexual abuse can also occur. There is some evidence that fomite spread is possible through the use of bidets, shared towels and undergarments.⁸⁶ The incubation period for HPV has been estimated at 1–20 months, but latency periods may be in excess of 2 years.⁸⁷ Although the vast majority of HPV disease results in transient lesions with a benign course, infection with certain subtypes of HPV (16, 18, 31, 33) can eventually lead to malignant metaplasia of the infected tissue.

Clinical lesions associated with HPV infections are only rarely present at birth or during the early neonatal period. Such lesions include anogenital warts (condyloma acuminata) and laryngeal papillomatosis. These lesions are more likely to become evident from 6 months to 2 years of age, and are believed to result from perinatal infection with a long latency period preceding clinical expression. An epidemiologic study of anogenital and laryngeal lesions in children under 13 years of age noted that the mean age of children with HPV was 4.5 years.⁸⁸ Given that the majority of cases of anogenital HPV occur beyond 2 years of age, and that only a minority of these are sexually transmitted, it appears that many anogenital and laryngeal HPV infections in children are the result of horizontal transmission that is nonsexual.

Cutaneous findings

Condyloma acuminata favor the mucocutaneous junctions and are soft, papillomatous pink to flesh-colored lesions that may be discrete or confluent, pedunculated or flat-topped (Fig. 13.16). Areas most frequently affected in infants include the perianal skin, glans penis, vulva, and vaginal introitus (Fig. 13.17). The usual interval between exposure and the development of lesions appears to be 1–8 months, with an average of 3 months; however it is believed that much longer latency periods, perhaps up to 2 years, can occur.^{89,90} Lesions presenting in the neonatal period may represent in utero or perinatal



Figure 13.16 Human papilloma virus infection. Congenital verrucous, filiform papules of the upper lip.



Figure 13.17 Human papilloma virus infection. Multiple flesh-colored, discrete, and coalescent verrucous papules in the perianal region. Several smaller, ovoid flat lesions can be seen peripheral to the perianal site.

exposure. Respiratory tract papillomas may affect the larynx, and less commonly the trachea, bronchial, and pulmonary epithelia. They are thought to be acquired by aspiration of infectious maternal vaginal and cervical secretions during labor. Such lesions usually present in infancy with hoarseness and respiratory distress.

Etiology and pathogenesis

HPV is a small (55 nm), non-enveloped, circular, double-stranded DNA virus. It is expressed exclusively in fully differentiated keratinocytes and cannot be perpetuated in tissue culture. Over 130 different subtypes possessing varied oncogenic potential and tissue tropism have been identified. Although the papilloma viruses are categorized as to mucosal or cutaneous tropism, this classification is not strict, as genital types may be found on the skin, and cutaneous subtypes have been identified in anogenital lesions, particularly in children.⁹¹ The viruses have also been classified as to their malignant potential. HPV 6 and 11 are considered low-risk subtypes, whereas HPV 16, 18, 31, and 33 have been associated with anogenital cancer. HPV 30 has been associated with oral and laryngeal carcinoma, as well as anogenital carcinoma.⁹¹



Figure 13.14 Coxsackie virus infection. Gray-pink vesicles on the dorsal hand of a young child. (Courtesy of Dr Erin Mathes and Dr Leonard Kristal.)

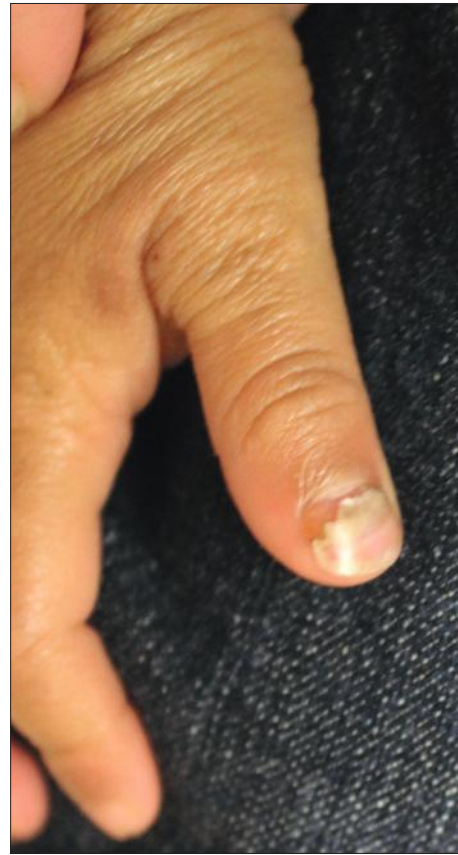


Figure 13.15 Onychomadesis in a young child following coxsackie virus infection.

HPV is one of the most common sexually transmitted diseases, and its incidence in infants and children probably reflects prevalence in the adult population.⁹² Most anogenital warts are subclinical and asymptomatic. The prevalence of genital lesions (condyloma) in the adult population is 0.6–13%, but molecular diagnostic studies have shown evidence of HPV infection in 11–80% of asymptomatic, sexually active young women.^{93–95} Transmission of infection may occur through vertical, innocent, and sexual contact. Subclinical infection of the cervix or vagina of a pregnant woman may lead to infection in her infant.⁹⁶ The virus can be transmitted from mother to fetus before or during birth, and the rate of perinatal transmission from genital HPV-positive mothers to the pharyngeal mucosa of their infants is approximately 30–50%.^{97,98} However, studies of mother–neonate pairs have demonstrated that even when there is transmission of virus, it is most often only transient and clinical disease is unlikely to occur.^{97–99}

Neonates appear to be at higher risk for exposure to HPV during vaginal delivery than during cesarean section.⁹⁷ However, infants born by cesarean section have been found to be HPV DNA-positive for the same type as their mothers.¹⁰⁰ Rare cases of anogenital warts present at birth following cesarean section delivery support the possibility of ascending infection.⁹⁸ Transplacental exposure would explain such findings, as would small amniotic tears or leaks. The risk of a child contracting laryngeal papillomatosis is quite small.

HPV DNA has been identified in hepatic tissue from four infants with extrahepatic biliary duct atresia and three with neonatal giant cell hepatitis. Concordant HPV types were found in the infants' mothers, supporting vertical transmission of the virus and its role in the pathologies noted in these infants.¹⁰¹

Epidermodysplasia verruciformis is a rare inherited disorder associated with immunodeficiency that leads to a chronic susceptibility to infection with certain subtypes of HPV. Lesions often resemble flat warts and malignant transformation can occur in later life.

Diagnosis

The clinical appearance of anogenital warts is usually diagnostic. A careful maternal history, including prior genital lesions and abnormal PAP smears, should be obtained. However, a negative history and normal maternal examination do not rule out the possibility of HPV disease. A spontaneous remission rate as high as 67% has been reported for HPV infections,⁹² and subclinical infection of the cervix or vagina may be present.

Histopathologic examination of anogenital HPV lesions demonstrates a slightly thickened stratum corneum, papillomatosis, and acanthosis of the epithelium, and thickening and elongation of the rete ridges. The presence of large vacuolated cells (koilocytes) in the epithelium is a characteristic sign, but is absent in approximately 50% of biopsies. HPV typing using probes against the most commonly encountered types (6, 11, 16, 18, and 33) may be useful. Such typing can now be performed using paraffin sections from routinely fixed tissue samples. PCR evaluation of suspicious areas has also been performed using specimens obtained by swabbing the site with a simple cotton swab, but this technique is not standardly available.¹⁰⁸

Differential diagnosis

Sexual abuse should be considered in childhood HPV disease but is much less likely in the small infant. Condyloma lata should always be considered in the differential diagnosis.

Syphilitic lesions are usually moister, wider based, and frequently larger than anogenital HPV lesions. Infantile pyramidal protrusion consists of a soft tissue swelling covered by smooth erythematous skin on the perineal median raphe. These may be congenital, tend to be larger than anogenital HPV lesions, and possess a smoother surface and a broad base. Molluscum contagiosum lesions are generally smoother, with a dome-shaped configuration, and central umbilication. Pseudoverrucous papules and nodules occur following chronic irritant diaper dermatitis and can be mistaken for condyloma. Skin tags may also resemble condyloma acuminata, but are uncommon in the neonatal period, are flesh-colored, discrete, and do not spread.

Treatment

Prevention is the optimal approach, and the development of at least two human papilloma virus vaccines has increased the likelihood of success of this goal. One of these vaccines, Gardasil®, is effective against HPV types 6, 11, 16, and 18; it was FDA approved for vaccination of all females from 9–26 years in 2006 and all males from 9–26 years in 2009. This vaccine is effective only if given prior to exposure to the particular HPV subtypes represented, and therefore vaccination prior to sexual intercourse is recommended.

Many experts believe that treatment of these viral lesions may not always be necessary because warts are relatively asymptomatic, the spontaneous remission rate is quite high, and the cure rate with therapy low. However, it must be kept in mind that oncogenic forms (HPV 16, 18, 31, 33) can lead to anogenital cancers later in life. Fortunately, these subtypes are not usually found in childhood lesions. No easy, universally effective treatment exists. A number of therapeutic modalities have been used in adults and older children. These include liquid nitrogen, intralesional *Candida* antigen immunotherapy, podophyllin resin, trichloroacetic acid, cantharidin, podofilox, imiquimod 5% cream, sinecatechins and interferon. Physical destruction, including electrodesiccation, laser therapy, and simple excision, is an alternative therapy. The failure rate for treatment of HPV infections has been estimated at 25–50%, regardless of the method used.¹⁰² Vaccination to prevent acquisition of strains with neoplastic potential is the optimal approach.

Most experts opt for simple, less painful means of treatment in infants and young children. Agents frequently used for anogenital warts include podophyllin resin, trichloroacetic acid, and imiquimod cream. Sequential intralesional *Candida* injections are utilized for other sites. The family must be aware that frequent treatments are often required and that subclinical lesions in surrounding skin may become evident over time, despite the eradication of currently existing lesions.

Molluscum contagiosum

Molluscum contagiosum is a viral infection of the skin that most commonly affects young children, but can occur at any age. This disease is only rarely noted in the neonatal period, but lesions have been documented within the first week of life.¹⁰³ A retrospective chart review of 302 patients found that less than 1% of affected patients were under 1 year and 28% of all affected patients were less than 36 months of age. The majority of patients who contracted the disease had fewer than 15 lesions, and children with atopic dermatitis were at higher risk for an increased number of lesions.¹⁰⁴

Cutaneous findings

Molluscum lesions initially appear as small pink or flesh-colored pinpoint papules, which gradually enlarge and assume a pearly or white dome-shaped appearance. The papules are usually 1–5 mm in size, but giant lesions in excess of 1 cm can occur. The lesions tend to cluster, and more commonly appear on the trunk and in intertriginous areas such as the antecubital and popliteal fossae and axillae. Rarely, lesions may develop on the palms, soles, or mucous membranes. An eczematoid, red, scaling patch may surround the papules and is termed molluscum dermatitis. Autoinoculation from scratching or shaving may occur.

There are rare reports of molluscum contagiosum in the newborn (Fig. 13.18). Mandel and Lewis¹⁰³ reported an infant who developed two thigh papules at 1 week of life, and another author documented multiple scalp lesions in a 6-week-old.¹⁰⁵ However, in a series of five women with genital molluscum lesions at the time of delivery, none of their infants developed molluscum.¹⁰⁶

Etiology and pathogenesis

Molluscum contagiosum is caused by a large, approximately 300 nm, brick-shaped poxvirus, which contains double-stranded DNA. At least 43 different DNA subtypes have been identified. The entire genetic sequence of MCV type 1 has been determined, and there appears to be considerable protein homology with the smallpox virus. The virus does not grow in tissue culture, and an animal model does not exist.

Molluscum has a worldwide distribution, but is most common in tropical countries. Spread is through direct (including sexual) contact with infected persons, contaminated items, or by means of autoinoculation. The incubation period is estimated at 2 weeks to 6 months. The duration of disease is quite variable and may last just a few weeks or more than 1 year. Incidence peaks in early childhood and again in young adults, as a result of sexual transmission. An increased incidence has been noted in wrestlers and swimmers, and outbreaks have occurred in pools and waterparks.¹⁰⁷ The disease has only rarely been noted in neonates, and it has been hypothesized that transplacental maternally derived antibody may be protective, but it can be seen in older infants. The immunocompromised, especially those with HIV infection, are subject to particularly extensive and prolonged infections that commonly involve the face. Patients with atopic dermatitis also appear to have more prolonged infections.

Diagnosis

The diagnosis is easily established when classic dome-shaped opalescent lesions with central umbilication are present. A curd-like material can be expressed from the central core and examined for the presence of molluscum bodies. These appear as monomorphous ovoid granular structures, and are best visualized with Wright's or Giemsa stains; (KOH) potassium hydroxide staining is also an option. Histopathologic evaluation of a lesion will reveal large intracytoplasmic inclusion bodies within suprabasilar epithelial cells and lobular proliferation of the epidermis.

Differential diagnosis

Cutaneous cryptococcal lesions are occasionally mistaken for molluscum contagiosum in immunocompromised patients.

Small lesions may be mistaken for common or flat warts. Giant molluscum lesions can resemble juvenile xanthogranuloma or Langerhans' cell histiocytosis. Large inflamed lesions may resemble furuncles. The differential diagnosis for atypical giant lesions includes a number of neoplastic disorders, and biopsy is indicated in such cases.

Treatment

Molluscum is generally self-limited and frequently does not require therapy. Instances where intervention may be necessary include conjunctival lesions, which may damage the cornea, irritated, bleeding, or rapidly spreading lesions, and cosmetically disfiguring lesions, particularly in the immunosuppressed patient. Genital lesions are usually treated to prevent spread. A number of therapeutic modalities are used, including physical agents such as cryotherapy and curettage. Topical chemical treatments include cantharidin 0.7% in collodion, imiquimod 5%, podophyllin, salicylic acid, tretinoin, and silver nitrate. Cantharidin is commonly used, and is applied with a wooden applicator to each site, taking care to avoid mucosal, intertriginous, and facial areas. The site is not occluded, and the family is instructed to wash the area in 2–6 h, depending on previous sensitivity to the agent. Repeat treatments are sometimes required. Adhesive tape occlusion and systemic cimetidine therapy have been utilized, with variable results. A local anesthetic consisting of topical lidocaine (LMX-4) may be applied prior to curettage. Families should be advised that multiple visits and treatments may be required and that spread of infection may occur through shared baths, towels, and swimming pools. Genital lesions are not uncommon in young children and are thought to be the result of autoinoculation. The issue of sexual abuse may be raised in older children, but supporting evidence should be documented prior to referral, as nonsexually transmitted genital involvement is often seen in childhood infections.

Viral exanthems in infants and toddlers

Viral illnesses commonly affect infants and toddlers and can be distinguished by the morphology and distribution of skin lesions (Table 13.5), as well as associated symptoms.

MEASLES (RUBEOLA)

Measles results from infection with a single-stranded RNA paramyxovirus, genus *Morbillivirus*. Transmission peaks in the late winter and early spring. It is highly contagious via respiratory droplets. The measles vaccination program has induced a greater than 99% decrease in the reported incidence of measles; however new measles infections in the United States continue to occur.¹⁰⁸ Although herd immunity provides protection, it is important for practitioners to recognize this disease, which may affect infants as their passive immunity wanes before their eligibility for vaccination at 1 year of age and may also affect those who forgo immunization. Measles infection can be complicated by pneumonia, gastroenteritis, myocarditis, and encephalitis.

Clinical findings

Measles typically presents with cough, coryza, conjunctivitis and fever. Blue-white papules on erythematous buccal mucosa



Figure 13.18 Solitary molluscum contagiosum lesion on the scalp of an infant. (Courtesy of Dr Angela Hernandez-Martin.)

TABLE 13.5 Skin findings of viral disease in children 1–24 months of age

Infection	Skin findings
Measles (rubeola)	Koplik spots (transient blue-gray to white papules on buccal mucosa across from second molar), erythematous macules and papules starting on face and behind ears and spreading down trunk
Rubella (German measles)	Forchheimer spots (transient red papules on soft palate), pink macules and papules starting on face and spreading down trunk (measles-like), lymphadenopathy
Roseola	Blanchable pink macules and papules on trunk which erupt after high fever (>103°F) breaks
Parvovirus B19	Rosy pink patches on cheeks ('slapped cheeks') and lacy interconnecting pink macules on extremities, papules and purpura on the hands and feet (young infants)
Enterovirus	Herpangina: erythematous round punched-out erosions on soft palate Hand, foot, and mouth disease: oval superficial vesicles on hands, feet, knees, buttocks and erosions of oral mucosa, post-illness nail changes including Beau's lines and onychomadesis
Human papillomavirus	Skin-toned verrucous, flat-topped and filiform papules on skin, genital mucosa, or respiratory mucosa
Molluscum contagiosum	Pink to skin-toned dome shaped papules with central umbilication on skin

directly across from premolar teeth, termed Koplik's spots, can be seen at the onset of these symptoms and are pathognomonic for the disease. Koplik's spots typically fade as the rash develops, so their absence does not rule out the diagnosis. The skin eruption begins about 2–4 days after the prodromal symptoms with erythematous macules and papules (morbilliform) on the temples and behind the ears, which then progresses downward from the face to involve the trunk and extremities.

Differential diagnosis

Morbilliform drug eruptions, Kawasaki disease, and other viral exanthems (e.g., rubella) may enter the differential diagnosis of measles. In most cases, the clinical history of symptoms and evolution of the rash will help differentiate.

Diagnosis

Most commonly, measles can be diagnosed based on the history and clinical findings; however, laboratory confirmation is available through serologies and PCR.

Treatment

Supportive care is generally the only intervention indicated as there is no specific treatment for measles. In developing countries, vitamin A supplementation has been shown to reduce measles-related morbidity and mortality.¹⁰⁹ While recognizing that there are limitations in the available data, the American Academy of Pediatrics recommends that vitamin A supplementation be considered in any infant (ages 6 months–2 years) hospitalized for measles and associated complications, as well as in infants more than 6 months of age diagnosed with measles who are recent immigrants, or who have immunodeficiency,

malnutrition, diseases which impair intestinal absorption (e.g., cystic fibrosis, short gut syndrome), or ophthalmologic signs of vitamin A deficiency (Bitot's spots, xerophthalmia, night blindness).¹¹⁰ The need for, and safety of, vitamin A supplementation in infants with measles who are <6 months old has not been established.¹¹⁰

RUBELLA (GERMAN MEASLES)

Rubella is caused by infection with the rubella virus, an enveloped, single-stranded RNA togavirus. Similar to measles, the illness peaks in incidence in late winter and spring and is transmitted via the respiratory route. Rubella is included in the MMR vaccine, which infants should receive at 12 months with a booster to follow at 4 years. The vaccination schedule has been successful in the control of rubella. The Centers for Disease Control and Prevention determined that the USA achieved endemic rubella elimination in 2001, and more recent evidence supports that the elimination of endemic rubella is being maintained.¹¹¹ However, it is important for practitioners to recognize this illness, as it remains endemic in many other parts of the world and susceptible or unvaccinated infants may potentially be exposed through contact with family members who travel globally. For example, exposure to rubella through air travel has been reported, although contact-tracing revealed no cases of a rubella-like rash.¹¹²

Clinical manifestations include low-grade fevers, mild upper respiratory symptoms, and lymphadenopathy, especially in the posterior head and neck lymphatic chains. In some cases, transient red papules termed 'Forchheimer spots' may be seen on the soft palate early in the infection. The skin eruption often mimics measles, with pink macules and papules starting on the face and spreading downward to the trunk and extremities. The exanthem fades in about 3 days, so the illness is sometimes referred to as '3-day measles'. Care is supportive and the symptoms tend to be mild; however, care must be taken to isolate children with suspected rubella from expectant mothers who are either non-immune or do not know their rubella immunity status to prevent congenital rubella syndrome (see above).

ROSEOLA (EXANTHEM SUBITUM, SIXTH DISEASE)

Roseola is a mild viral illness that is very common in infants aged 6–12 months. It is attributed to human herpesvirus (HHV) type 6 or 7. HHV7 infections occur less often in children <24 months of age, and most roseola cases are associated with HHV6.¹¹³ Although nearly 90% of adults demonstrate serologic immunity to these ubiquitous viruses, only about one-third of infants develop the acute illness.

The infection manifests with 3–7 days of high fever (>103°F). Febrile seizures develop in up to 10–15% of affected infants. When the fever breaks, blanchable, pink macules and papules erupt on the face, trunk and extremities. The exanthem is asymptomatic and fades over hours to days. In the febrile stage, supportive care with antipyretics is indicated, but otherwise no treatment is required for this transient viral illness.

UNILATERAL LATEROOTHORACIC EXANTHEM

Unilateral laterothoracic exanthem (ULE), also known as asymmetric periflexural exanthem of childhood, is a distinct skin

eruption that can be seen in children ages 12–24 months. In a prospective study, the mean age of onset was 24.3 months.¹¹⁴ It begins with a unilateral truncal eruption that extends to the axilla or inguinal area. Less commonly, extremities may be involved. Lesion morphology varies and includes macules, papules, eczematous patches and rarely, vesicles and purpura. As the eruption progresses, it often expands to involve the contralateral side. Itching is present in about 50% of affected children. Antihistamines and topical steroids can be used to reduce symptoms, and the eruption self-resolves over 3–8 weeks.

A viral etiology for ULE is suspected, as it occurs in young children and may be associated with prodromal upper respiratory or gastrointestinal symptoms as well as low-grade fever. Studies have not been able to confirm a consistent etiologic agent, and ULE may reflect a reaction pattern to more than one microorganism.


GIANOTTI-CROSTI SYNDROME

Gianotti–Crosti syndrome (GCS), also known as papular acrodermatitis of childhood, is a symmetric eruption of monomorphic, flat-topped pink or pink-brown papules on the cheeks,

buttocks, and extensor extremities. Lesions range in size from 1–10 mm. Younger children tend to develop larger papules. The eruption typically lasts about 3 weeks, but clearance may be delayed as long as 2–3 months. Prodromal fever and upper respiratory symptoms occur prior to rash onset in many patients, and in some children lymphadenopathy, hepatomegaly, and splenomegaly develop. GCS occurs in infants aged 3–24 months, as well as in children and adolescents; most affected children are older than 12 months.

GCS has been reported to occur in association with Epstein–Barr virus (EBV), hepatitis B virus, cytomegalovirus, and coxsackie virus.¹¹⁵ In the USA, EBV is the most commonly associated viral infection and associated hepatitis B infection is rare.¹¹⁶ GCS has also been linked to immunizations for influenza, diphtheria, pertussis, polio, Bacillus Calmette–Guérin (BCG), and measles/mumps/rubella (MMR).¹¹⁷ Similar to ULE, GCS is considered an immune system mediated reaction pattern to viral infections or immunizations.

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Figures 6, 11, 12, 14, 15 and 18 are available online at [ExpertConsult.com](https://www.expertconsult.com) 

KEY REFERENCES

11. Hutto C, Arvin A, Jacobs R, et al. Intrauterine herpes simplex virus infections. *J Pediatr* 1987; 110(1):97–101.
14. American Academy of Pediatrics. Committee on Infectious Diseases. Herpes simplex, varicella-zoster infections, human immunodeficiency virus, and parvovirus. In: Pickering LK, Baker CJ, Kimberlin DW, et al, editors. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village: American Academy of Pediatrics; 2012. p. 398–408, 774–789, 419–439, 539–541.
17. Enders G, Miller E, Craddock-Watson J, et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet* 1994;343(8912):1548–51.
18. Kakourou T, Theodoridou M, Mostrou G, et al. Herpes zoster in children. *J Am Acad Dermatol* 1998;39:207–10.
34. Chaves SS, Lopez AS, Watson TL, et al. Varicella in infants after implementation of the US varicella vaccination program. *Pediatrics* 2011; 128(6):1071–7.
47. Prose NS. Cutaneous manifestations of HIV infection in children. *Dermatol Clin* 1991;9(3): 543–50.
76. Abzug MJ. Presentation, diagnosis, and management of enterovirus infections in neonates. *Paediatr Drugs* 2004;6(1):1–10.
83. Mancini AJ. Childhood exanthems: a primer and update for the dermatologist. *Adv Dermatol* 2000;16:3–38.
87. Siegfried EC. Warts on children: an approach to therapy. *Pediatr Ann* 1996;25(2):79–90.
117. Nelson JS, Stone MS. Update on selected viral exanthems. *Curr Opin Pediatr* 2000;12(4): 359–64.

REFERENCES

- Sullivan-Bolyai J, Hull HF, Wilson C, et al. Neonatal herpes simplex virus infection in King County, Washington. Increasing incidence and epidemiologic correlates. *JAMA* 1983;250(22):3059–62.
- Overall JC Jr. Herpes simplex virus infection of the fetus and newborn. *Pediatr Ann* 1994; 23(3):131–6.
- Brown ZA, Benedetti J, Ashley R, et al. Neonatal herpes simplex virus infection in relation to asymptomatic maternal infection at the time of labor. *N Engl J Med* 1991;324(18): 1247–52.
- Brown ZA, Wald A, Morrow RA, et al. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003;289(2):203–9.
- Cone RW, Hobson AC, Brown Z, et al. Frequent detection of genital herpes simplex virus DNA by polymerase chain reaction among pregnant women. *JAMA* 1994;272(10):792–6.
- ACOG Committee on Practice Bulletins. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Management of herpes in pregnancy. *Obstet Gynecol* 2007;109(6):1489–98.
- Pinninti SG, Angara R, Feja KN, et al. Neonatal herpes disease following maternal antenatal antiviral suppressive therapy: a multicenter case series. *J Pediatr* 2012;161(1):134–8.
- Siebert OF Jr, Fulginiti VA, Brazie J, et al. In utero infection of the fetus by herpes simplex virus. *J Pediatr* 1966;69(1):30–4.
- South MA, Tompkins WA, Morris CR, et al. Congenital malformation of the central nervous system associated with genital type (type 2) herpesvirus. *J Pediatr* 1969;75(1): 13–18.
- Sullender WM, Miller JL, Yasukawa LL, et al. Humoral and cell-mediated immunity in neonates with herpes simplex virus infection. *J Infect Dis* 1987;155(1):28–37.
- Hutto C, Arvin A, Jacobs R, et al. Intrauterine herpes simplex virus infections. *J Pediatr* 1987; 110(1):97–101.
- Honig PJ, Brown D. Congenital herpes simplex virus infection initially resembling epidermolysis bullosa. *J Pediatr* 1982;101(6):958–60.
- Johansson AB, Rassart A, Blum D, et al. Lower-limb hypoplasia due to intrauterine infection with herpes simplex virus type 2: possible confusion with intrauterine varicella-zoster syndrome. *Clin Infect Dis* 2004;38(7):e57–62.
- American Academy of Pediatrics. Committee on Infectious Diseases. Herpes simplex, varicella-zoster infections, human immunodeficiency virus, and parvovirus. In: Pickering LK, Baker CJ, Kimberlin DW, et al, editors. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village: American Academy of Pediatrics; 2012. p. 398–408, 774–789, 419–439, 539–541.
- Kimberlin DW, Whitley RJ, Wan W, et al. Oral acyclovir suppression and neurodevelopment after neonatal herpes. *N Engl J Med* 2011; 365(14):1284–92.
- Kimberlin DW, Jacobs RE, Weller S, et al. Pharmacokinetics and safety of extemporaneously compounded valacyclovir oral suspension in pediatric patients from 1 month through 11 years of age. *Clin Infect Dis* 2010;50(2): 221–8.
- Enders G, Miller E, Craddock-Watson J, et al. Consequences of varicella and herpes zoster in pregnancy: prospective study of 1739 cases. *Lancet* 1994;343(8912):1548–51.
- Kakourou T, Theodoridou M, Mostrou G, et al. Herpes zoster in children. *J Am Acad Dermatol* 1998;39:207–10.
- Salzman MB, Sood SK. Congenital anomalies resulting from maternal varicella at 25 1/2 weeks of gestation. *Pediatr Infect Dis J* 1992; 11(6):504–5.
- Koren G. Congenital varicella syndrome in the third trimester. *Lancet* 2005;366(9497): 1591–2.
- Birthistle K, Carrington D. Fetal varicella syndrome – a reappraisal of the literature. A review prepared for the UK Advisory Group on Chickenpox on behalf of the British Society for the Study of Infection. *J Infect* 1998; 36(Suppl. 1):25–9.
- Harris RE, Rhoades ER. Varicella Pneumonia Complicating Pregnancy. Report of a Case and Review of Literature. *Obstet Gynecol* 1965;25: 734–40.
- Chapman SJ. Varicella in pregnancy. *Semin Perinatol* 1998;22(4):339–46.
- Hartung J, Enders G, Chaoui R, et al. Prenatal diagnosis of congenital varicella syndrome and detection of varicella-zoster virus in the fetus: a case report. *Prenat Diagn* 1999;19(2):163–6.
- Mouly F, Mirlesse V, Meritet JF, et al. Prenatal diagnosis of fetal varicella-zoster virus infection with polymerase chain reaction of amniotic fluid in 107 cases. *Am J Obstet Gynecol* 1997;177(4):894–8.
- Pretorius DH, Hayward I, Jones KL, et al. Sonographic evaluation of pregnancies with maternal varicella infection. *J Ultrasound Med* 1992;11(9):459–63.
- Verstraeten H, Vanzieleghem B, Defoort P, et al. Prenatal ultrasound and magnetic resonance imaging in fetal varicella syndrome: correlation with pathology findings. *Prenat Diagn* 2003;23(9):705–9.
- Gershon AA. Chicken pox, measles, and mumps. *Infect Dis Fetus Newborn* 1995;4: 578–83.
- Miller E, Craddock-Watson JE, Ridehalgh MK. Outcome in newborn babies given anti-varicella-zoster immunoglobulin after perinatal maternal infection with varicella-zoster virus. *Lancet* 1989;2(8659):371–3.
- Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: Conclusions from the international acyclovir pregnancy registry, 1984–1999. *Birth Defects Res A Clin Mol Teratol* 2004;70(4):201–7.
- Singalavanija S, Limpongpanurak W, Horpoapan S, et al. Neonatal varicella: a report of 26 cases. *J Med Assoc Thai* 1999;82(10):957–62.
- Detlefs RL, Frieden IJ, Berger TG, et al. Eosinophil fluorescence: a cause of false positive slide tests for herpes simplex virus. *Pediatr Dermatol* 1987;4(2):129–33.
- Bendig JW, Meurisse EV, Anderson F, et al. Neonatal varicella despite maternal immunity. *Lancet* 1998;352(9145):1985–6.
- Chaves SS, Lopez AS, Watson TL, et al. Varicella in infants after implementation of the US varicella vaccination program. *Pediatrics* 2011; 128(6):1071–7.
- Galea SA, Sweet A, Beninger P, et al. The safety profile of varicella vaccine: a 10-year review. *J Infect Dis* 2008;197(Suppl. 2):S165–9.
- Klassen TP, Hartling L, Wiebe N, et al. Acyclovir for treating varicella in otherwise healthy children and adolescents. *Cochrane Database Syst Rev* 2005(4):CD002980.
- Ross SA, Boppana SB. Congenital cytomegalovirus infection: outcome and diagnosis. *Semin Pediatr Infect Dis* 2005;16(1):44–9.
- Demmler GJ. Infectious Diseases Society of America and Centers for Disease Control. Summary of a workshop on surveillance for congenital cytomegalovirus disease. *Rev Infect Dis* 1991;13(2):315–29.
- Schleiss MR. Antiviral therapy of congenital cytomegalovirus infection. *Semin Pediatr Infect Dis* 2005;16(1):50–9.
- Kimberlin DW, Lin CY, Sanchez PJ, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. *J Pediatr* 2003;143(1):16–25.
- Acosta EP, Brundage RC, King JR, et al. Ganciclovir population pharmacokinetics in neonates following intravenous administration of ganciclovir and oral administration of a liquid valganciclovir formulation. *Clin Pharmacol Ther* 2007;81(6):867–72.
- Cooper LZ, Preblud SR, Alford CA. Rubella. In: Remington JS, Klein JO, editors. *Infectious diseases of the fetus and newborn infant*. 6th ed. Philadelphia: WB Saunders; 2006. p. 893–926.
- Sanchez PJ, Demmler-Harrison GJ. Viral infections of the fetus and neonate. In: Feigin RD, Cherry JD, Demmler-Harrison GJ, et al, editors. *Textbook of pediatric infectious diseases*. 6th ed. Philadelphia: WB Saunders; 2009. p. 895–941.
- Burchett SK, Pizzo PA. HIV infection in infants, children, and adolescents. *Pediatr Rev* 2003;24(6):186–94.
- Pahwa S, Kaplan M, Fikrig S, et al. Spectrum of human T-cell lymphotropic virus type III infection in children. Recognition of symptomatic, asymptomatic, and seronegative patients. *JAMA* 1986;255(17):2299–305.
- Shetty D, Giri N, Gonzalez CE, et al. Invasive aspergillosis in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 1997;16(2):216–21.
- Prose NS. Cutaneous manifestations of HIV infection in children. *Dermatol Clin* 1991; 9(3):543–50.
- Centers for Disease Control. HIV/AIDS surveillance report. Cancer as AIDS-defining illness. Washington: CDC; 1993. p. 1–18.
- Athale UH, Patil PS, Chintu C, et al. Influence of HIV epidemic on the incidence of Kaposi's sarcoma in Zambian children. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; 8(1):96–100.
- Gutierrez-Ortega P, Hierro-Orozco S, Sanchez-Cisneros R, et al. Kaposi's sarcoma in a 6-day-old infant with human immunodeficiency virus. *Arch Dermatol* 1989;125(3):432–3.
- Mueller BU, Butler KM, Higham MC, et al. Smooth muscle tumors in children with human immunodeficiency virus infection. *Pediatrics* 1992;90(3):460–3.
- Straka BF, Whitaker DL, Morrison SH, et al. Cutaneous manifestations of the acquired

- immunodeficiency syndrome in children. *J Am Acad Dermatol* 1988;18:1089–102.
53. Marion RW, Wiznia AA, Hutcheon RG, et al. Fetal AIDS syndrome score. Correlation between severity of dysmorphism and age at diagnosis of immunodeficiency. *Am J Dis Child* 1987;141(4):429–31.
 54. Gelber RD, Shapiro DE. Mode of delivery and the risk of vertical transmission of HIV-1. *N Engl J Med* 1999;341(3):206–7.
 55. Meyer MP, Latief Z, Haworth C, et al. Symptomatic HIV infection in infancy – clinical and laboratory markers of infection. *S Afr Med J* 1997;87(2):158–62.
 56. Culnane M, Fowler M, Lee SS, et al. Lack of long-term effects of in utero exposure to zidovudine among uninfected children born to HIV-infected women. *Pediatric AIDS Clinical Trials Group Protocol 219/076 Teams. JAMA* 1999;281(2):151–7.
 57. Vogel H, Kornman M, Ledet SC, et al. Congenital parvovirus infection. *Pediatr Pathol Lab Med* 1997;17(6):903–12.
 58. Valeur-Jensen AK, Pedersen CB, Westergaard T, et al. Risk factors for parvovirus B19 infection in pregnancy. *JAMA* 1999;281(12):1099–105.
 59. Brown KE, Green SW, Antunez de Mayolo J, et al. Congenital anaemia after transplacental B19 parvovirus infection. *Lancet* 1994;343(8902):895–6.
 60. Tiessen RG, van Elsacker-Niele AM, Vermeij-Keers C, et al. A fetus with a parvovirus B19 infection and congenital anomalies. *Prenat Diagn* 1994;14(3):173–6.
 61. Conroy JA, Torok T, Andrews PI. Perinatal encephalopathy secondary to in utero human parvo B19 infection [abstract 7365]. *Neurology* 1993;43:A346.
 62. Van Elsacker-Niele AM, Salimans MM, Weiland HT, et al. Fetal pathology in human parvovirus B19 infection. *Br J Obstet Gynaecol* 1989;96(7):768–75.
 63. Miller E, Fairley CK, Cohen BJ, et al. Immediate and long term outcome of human parvovirus B19 infection in pregnancy. *Br J Obstet Gynaecol* 1998;105(2):174–8.
 64. Auerbach AD, Verlander PC, Brown KE, et al. New molecular diagnostic tests for two congenital forms of anemia. *J Clin Lab Anal* 1997;11(1):17–22.
 65. Minowa H, Nishikubo T, Uchida Y, et al. Neonatal erythema infectiosum. *Acta Paediatr Jpn* 1998;40(1):88–90.
 66. Prospective study of human parvovirus (B19) infection in pregnancy. Public Health Laboratory Service Working Party on Fifth Disease. *BMJ* 1990;300(6733):1166–70.
 67. Fairley CK, Smoleniec JS, Caul OE, et al. Observational study of effect of intrauterine transfusions on outcome of fetal hydrops after parvovirus B19 infection. *Lancet* 1995;346(8986):1335–7.
 68. Levy R, Weissman A, Blomberg G, et al. Infection by parvovirus B 19 during pregnancy: a review. *Obstet Gynecol Surv* 1997;52(4):254–9.
 69. Hsieh MY, Huang PH. The juvenile variant of papular-purpuric gloves and socks syndrome and its association with viral infections. *Br J Dermatol* 2004;151(1):201–6.
 70. Sasidharan CK, Sugathan P, Mampilly N, et al. Red baby syndrome a new disease due to parvovirus B-19 observed in Kerala. *Indian J Pediatr* 2009;76(3):309–12.
 71. Amabile N, Fraisse A, Bouvenot J, et al. Outcome of acute fulminant myocarditis in children. *Heart* 2006;92(9):1269–73.
 72. Dettmeyer R, Baasner A, Schlamann M, et al. Role of virus-induced myocardial affections in sudden infant death syndrome: a prospective postmortem study. *Pediatr Res* 2004;55(6):947–52.
 73. Ballou WR, Reed JL, Noble W, et al. Safety and immunogenicity of a recombinant parvovirus B19 vaccine formulated with MF59C.1. *J Infect Dis* 2003;187(4):675–8.
 74. Bernstein DI, El Sahly HM, Keitel WA, et al. Safety and immunogenicity of a candidate parvovirus B19 vaccine. *Vaccine* 2011;29(43):7357–63.
 75. Verboon-Macielek MA, Krediet TG, Gerards LJ, et al. Severe neonatal parechovirus infection and similarity with enterovirus infection. *Pediatr Infect Dis J* 2008;27(3):241–5.
 76. Abzug MJ. Presentation, diagnosis, and management of enterovirus infections in neonates. *Paediatr Drugs* 2004;6(1):1–10.
 77. Abzug MJ, Levin MJ, Rotbart HA. Profile of enterovirus disease in the first two weeks of life. *Pediatr Infect Dis J* 1993;12(10):820–4.
 78. Nuovo GJ, Cooper LD, Bartholomew D. Histologic, infectious, and molecular correlates of idiopathic spontaneous abortion and perinatal mortality. *Diagn Mol Pathol* 2005;14(3):152–8.
 79. Sanchez PJ, Demmler-Harrison GJ. Viral infections of the fetus and neonate. In: Feigin RD, Cherry JD, Demmler-Harrison GJ, editors. *Textbook of pediatric infectious diseases*. 6th ed. Philadelphia: WB Saunders; 2009. p. 895–941.
 80. Modlin JF. Update on enterovirus infections in infants and children. *Adv Pediatr Infect Dis* 1996;12:155–80.
 81. Sawyer MH. Enterovirus infections: diagnosis and treatment. *Pediatr Infect Dis J* 1999;18(12):1033–9.
 82. Abzug MJ, Keyserling HL, Lee ML, et al. Neonatal enterovirus infection: virology, serology, and effects of intravenous immune globulin. *Clin Infect Dis* 1995;20(5):1201–6.
 83. Mancini AJ. Childhood exanthems: a primer and update for the dermatologist. *Adv Dermatol* 2000;16:3–38.
 84. Centers for Disease Control and Prevention (CDC). Notes from the field: severe hand, foot, and mouth disease associated with coxsackievirus A6 – Alabama, Connecticut, California, and Nevada, November 2011–February 2012. *MMWR Morb Mortal Wkly Rep* 2012;61(12):213–14.
 85. Mathes E, Frieden I, Glaser C, et al. Characterization of cutaneous findings in the enterovirus outbreak of 2011–2012. 38th Annual Meeting of the Society for Pediatric Dermatology, San Francisco, 2012.
 86. Pacheco B, DiPaola G, Ribas J, et al. Vulvar infections caused by human papilloma virus in children and adolescents without sexual contact. *Adolesc Pediatr Gynecol* 1991;4:136–42.
 87. Siegfried EC. Warts on children: an approach to therapy. *Pediatr Ann* 1996;25(2):79–90.
 88. Sinclair KA, Woods CR, Kirse DJ, et al. Anogenital and respiratory tract human papillomavirus infections among children: age, gender, and potential transmission through sexual abuse. *Pediatrics* 2005;116(4):815–25.
 89. Barrett TJ, Silbar JD, McGinley JP. Genital warts – a venereal disease. *J Am Med Assoc* 1954;154(4):333–4.
 90. Oriel JD. Natural history of genital warts. *Br J Vener Dis* 1971;47(1):1–13.
 91. Majewski S, Jablonska S. Human papillomavirus-associated tumors of the skin and mucosa. *J Am Acad Dermatol* 1997;36(5 Pt 1):659–85.
 92. Allen AL, Siegfried EC. The natural history of condyloma in children. *J Am Acad Dermatol* 1998;39(6):951–5.
 93. Moscicki AB. Human papillomavirus infections. *Adv Pediatr* 1992;39:257–81.
 94. Schneider A, Koutsky LA. Natural history and epidemiological features of genital HPV infection. *IARC Sci Publ* 1992;119:25–52.
 95. Brown DR, Shew ML, Qadadri B, et al. A longitudinal study of genital human papillomavirus infection in a cohort of closely followed adolescent women. *J Infect Dis* 2005;191(2):182–92.
 96. Mazzatenta C, Fimiani M, Rubegni P, et al. Vertical transmission of human papillomavirus in cytologically normal women. *Genitourin Med* 1996;72(6):445–6.
 97. Sedlacek TV, Lindheim S, Eder C, et al. Mechanism for human papillomavirus transmission at birth. *Am J Obstet Gynecol* 1989;161(1):55–9.
 98. Tseng CJ, Liang CC, Soong YK, et al. Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. *Obstet Gynecol* 1998;91(1):92–6.
 99. Tenti P, Zappatore R, Migliora P, et al. Perinatal transmission of human papillomavirus from gravidas with latent infections. *Obstet Gynecol* 1999;93(4):475–9.
 100. Puranen MH, Yliskoski MH, Saarikoski SV, et al. Exposure of an infant to cervical human papillomavirus infection of the mother is common. *Am J Obstet Gynecol* 1997;176(5):1039–45.
 101. Drut R, Gomez MA, Drut RM, et al. Human papillomavirus, neonatal giant cell hepatitis and biliary duct atresia. *Acta Gastroenterol Latinoam* 1998;28(1):27–31.
 102. Hines JE, Ghim S, Jensen AB. Prospects for human papillomavirus vaccine development: emerging HPV vaccines. *Curr Opin Infect Dis* 1998;11(1):57–61.
 103. Mandel MJ, Lewis RJ. Molluscum contagiosum of the newborn. *Br J Dermatol* 1971;84(4):370–2.
 104. Dohil MA, Lin P, Lee J, et al. The epidemiology of molluscum contagiosum in children. *J Am Acad Dermatol* 2006;54(1):47–54.
 105. Young WJ. Molluscum contagiosum with unusual distribution. *Kentucky Med J* 1926:467.
 106. Wilkin JK. Molluscum contagiosum venereum in a women's outpatient clinic: a venereally transmitted disease. *Am J Obstet Gynecol* 1977;128(5):531–5.
 107. Castilla MT, Sanzo JM, Fuentes S. Molluscum contagiosum in children and its relationship to attendance at swimming-pools: an epidemiological study. *Dermatology* 1995;191(2):165.
 108. Centers for Disease Control and Prevention (CDC). Measles: United States, January–May 20, 2011. *MMWR Morb Mortal Wkly Rep* 2011;60(20):666–8.

109. D'Souza RM, D'Souza R. Vitamin A for the treatment of children with measles – a systematic review. *J Trop Pediatr* 2002;48(6):323–7.
110. American Academy of Pediatrics Committee on Infectious Diseases. Vitamin A treatment of measles. *Pediatrics* 1993;91(5):1014–15.
111. Reef SE, Redd SB, Abernathy E, et al. Evidence used to support the achievement and maintenance of elimination of rubella and congenital rubella syndrome in the United States. *J Infect Dis* 2011;204(Suppl. 2):S593–7.
112. Kim C, Chavez P, Pierce A, et al. Rubella contact tracing associated with air travel. *Travel Med Infect Dis* 2012;10(1):48–51.
113. Hall CB, Caserta MT, Schnabel KC, et al. Congenital infections with human herpesvirus 6 (HHV6) and human herpesvirus 7 (HHV7). *J Pediatr* 2004;145(4):472–7.
114. McCuaig CC, Russo P, Powell J, et al. Unilateral laterothoracic exanthem. A clinicopathologic study of forty-eight patients. *J Am Acad Dermatol* 1996;34(6):979–84.
115. Caputo R, Gelmetti C, Ermacora E, et al. Gianotti-Crosti syndrome: a retrospective analysis of 308 cases. *J Am Acad Dermatol* 1992;26(2 Pt 1):207–10.
116. Hofmann B, Schuppe HC, Adams O, et al. Gianotti-Crosti syndrome associated with Epstein-Barr virus infection. *Pediatr Dermatol* 1997;14(4):273–7.
117. Nelson JS, Stone MS. Update on selected viral exanthems. *Curr Opin Pediatr* 2000;12(4):359–64.

Fungal Infections, Infestations, and Parasitic Infections in Neonates and Infants

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Fungal infections

Infections caused by fungi and yeasts are common in neonates and infants. Among the most frequent are *Candida* infections such as thrush and diaper dermatitis. More extensive manifestations, such as congenital and systemic candidiasis, are much less common. Improvements in preterm infant survival due to advances in neonatal intensive care and an increase in bone marrow and organ transplantation have resulted in more frequent systemic fungal infections. *Aspergillus* is second only to *Candida* as a cause of opportunistic fungal infections in immunocompromised pediatric hosts. Zygomycosis and trichosporonosis are seen almost exclusively in premature infants. *Malassezia* species colonize the newborn skin and plays a role in a variety of clinical presentations such as neonatal cephalic pustulosis, tinea versicolor, or fungemia. Dermatophyte infections (mainly tinea capitis and tinea corporis) are the predominant cutaneous fungal infections during infancy in otherwise healthy infants and children.

CANDIDIASIS

Epidemiology and pathogenesis

Candida is a common fungal pathogen. In newborns, infection may be acquired vertically from the mother or horizontally by nosocomial transmission in the nursery.¹ The increasing use of antifungal prophylaxis with azoles has changed the epidemiology of candidemia in immunocompromised pediatric patients. *C. albicans* is responsible for approximately 45% of neonatal fungal infections, while non-*albicans* candidal species are increasing in incidence.² Other *Candida* species associated with neonatal disease include *C. tropicalis*, *C. parapsilosis*, *C. lusitanae*, and *C. glabrata*. Normally, these yeasts are saprophytes, inhabiting the skin or gastrointestinal tract without invasion unless host defenses are altered. *Candida* spp. may also colonize endotracheal tubes and catheters without causing systemic illness, but associated clinical illness is common in very low-birthweight (VLBW) infants.³ In extremely low-birthweight (ELBW) infants (<1000 g), invasive candidiasis is more common. In one prospective study, 7% of 4379 infants had *Candida* isolated from blood or cerebrospinal fluid.⁴

Virulence mechanisms associated with *Candida* infections include fungal proteinase, increased adherence of yeast to epithelial cells due to similarity to mammalian cell ligands, and resistance to neutrophil ingestion of hyphal forms.⁵ Secretory IgA, functional T lymphocytes, and phagocytic cells are important in defense against *Candida* infections. Hence, there is increased susceptibility to these infections in patients with

secretory IgA deficiency, primary T-cell deficiency such as DiGeorge syndrome, severe combined immunodeficiency, chronic granulomatous disease, myeloperoxidase deficiency, and human immunodeficiency virus (HIV) infection. Recurrent or persistent yeast infections can be presenting symptoms of immunodeficiency. Host resistance to fungal infections also depends on activated macrophages, which in turn rely on T-lymphocyte release of interferon (IFN)- γ . Incomplete activation of macrophages by IFN in neonates⁶ contributes to increased susceptibility to invasive fungal disease.

Predisposing factors for *Candida* infections include excessive humidity, maceration, diabetes, and broad-spectrum antibiotics. Risk factors for systemic candidiasis in neonates include low birthweight, prematurity, broad-spectrum antibiotic therapy, indwelling catheters, prolonged endotracheal intubation, tracheostomy, prior fungal colonization, gastrointestinal pathology or abdominal surgery, enteral feeding, immunosuppression, defective neutrophil function or neutropenia, and steroid therapy.^{7–13} Similarly, pediatric patients with hematologic malignancies and neutropenia, short bowel syndrome with central vascular catheters or recent surgery or trauma (namely gastrointestinal/abdominal) are at increased risk of invasive candidiasis.²

Various techniques in addition to culture are used to evaluate the epidemiology of fungal pathogens. They include polymerase chain reaction (PCR), restriction fragment endonuclease digestion of chromosomal DNA, electrophoretic karyotyping, and Southern blot hybridization analysis using DNA probes, β -glucan assay (β -D-glucan is a major component of the fungal cell wall) and gas chromatography mass spectrometry for D-arabinitol (a major metabolite of most *Candida* species).^{1,14}

Clinical presentations of candidal infections are discussed in this chapter, followed by diagnostic and treatment recommendations.

Congenital candidiasis

Congenital candidiasis (CC) refers to *Candida* infection acquired in utero and presenting with symptoms in the first days of life.¹⁵ Classic congenital candidiasis presents as a diffuse cutaneous infection, presumed to arise from an ascending intrauterine chorioamnionitis. The typical patient is an otherwise healthy term neonate who, within the first 12 h of life, develops a monomorphous papulovesicular eruption that is intensely erythematous (Figs. 14.1, 14.2, 14.3) progressing to pustules, crusting and desquamation. Any area of the body surface, including the face, palms, and soles, can be involved, and widespread involvement is often evident (Fig. 14.4). *Candida* paronychia and onychomycosis have been reported.^{14–17}



Figure 14.2 Congenital candidiasis. Diffusely distributed, distinct pustules.



Figure 14.3 Congenital candidiasis.



Figure 14.1 Congenital candidiasis. Diffuse erythematous, pustular eruption.



Figure 14.4 Congenital candidiasis. Palmar pustules with erythema.

Congenital candidiasis is surprisingly uncommon given the 33% rate of vaginal colonization with *Candida* in pregnant women.⁷ The presence of a foreign body in the maternal uterus or cervix is a risk factor for CC.¹⁵ In the majority of term infants, systemic dissemination of CC is rare. The prognosis of a term infant with CC is excellent, with rapid clearance of the eruption using topical treatment. Occasionally, CC can present as pneumonia and sepsis without cutaneous manifestations.¹⁸ CC with systemic involvement is more commonly seen in premature, low-birthweight infants (<1500 g).^{15,19–21} Skin findings in these infants may be variable, with a burn-like dermatitis (similar to staphylococcal scalded skin syndrome) in addition to the usual red scaly or vesiculopustular eruption (Fig. 14.5).¹⁵ A widespread rash in a premature or ill-appearing infant, respiratory distress in the immediate postnatal period, leukocytosis, or

hyperglycemia should alert the physician to the possibility of systemic candidiasis despite negative blood cultures.^{15,21,22}

Systemic candidiasis

Systemic candidiasis (SC), defined as *Candida* infection in an otherwise sterile body fluid such as blood, urine, or cerebrospinal fluid, affects 2–7% of VLBW newborns.^{4,8,23} Skin manifestations occur in up to 60% of these infants.²² These infections can be acquired in utero (CC) or postnatally. In a multicenter prospective study, median gestational age and birthweight of neonatal invasive candidiasis was 30 weeks and 740 g, respectively.² Only half of these patients had a central venous catheter at the time of diagnosis. Baley and Silverman²³ described skin manifestations of VLBW infants with SC to include an extensive burn-like dermatitis followed by desquamation, progressive diaper dermatitis involving papules and pustules, and isolated diaper rash with or without thrush (Fig. 14.6).²³ Cutaneous abscesses at the site of intravascular catheters may also be seen.⁷ Systemic signs include apnea, bradycardia, abdominal distension, guaiac-positive stools, hyperglycemia, temperature instability, leukemoid reaction, and hypotension.^{7,8,24} During childhood, invasive candidiasis occurs in immunocompromised individuals, especially those having had a central vascular catheter placed within 7 days of diagnosis.² After hematopoietic stem cell transplantation, the median time to invasive candidiasis diagnosis is 74.5 days.² Systemic candidiasis in immunocompromised children presents as randomly distributed deep, firm and erythematous papules and nodules.

Invasive fungal dermatitis

Invasive fungal dermatitis (IFD) is a clinicopathologic entity of erosive crusting lesions in VLBW infants. It is described by Rowen and colleagues²⁵ as a primary skin condition that leads to secondary dissemination and systemic disease. It is primarily due to *Candida albicans* or other *Candida* species. *Aspergillus*, *Trichosporon asahii*, and *Curvularia* are also etiologic agents of invasive fungal dermatitis. Skin biopsy demonstrates fungal invasion beyond the stratum corneum, well into the epidermis, and at times extending into the dermis. Onset several days after birth, the presence of erosions and crusts, and typical histologic findings help to differentiate IFD from congenital candidiasis. Risk factors include extreme prematurity (<25 weeks' gestational age), vaginal birth, steroid administration, and hyperglycemia.²⁵

Localized candidiasis

Oral candidiasis (thrush). Acute oral candidiasis appears on the oropharyngeal mucosa as white adherent curd-like plaques resembling milk or formula (Fig. 14.6). Plaques can be scraped off only with difficulty, leaving a bright erythematous base (pseudomembranous and erythematous forms, respectively). Extensive infection can lead to feeding difficulties, particularly if the esophagus is involved.⁷ Perlèche is a candidal infection involving the lateral angles of the mouth.

Candida diaper dermatitis. *Candida* infection of the diaper area may occur alone or in conjunction with thrush. Bright, erythematous plaques, papules, and pustules affect the moist intertriginous areas of the perineum, with a predilection for inguinal creases. White scale and satellite pustules are common along the periphery, often prominent at the border of involved



Figure 14.8 Candidal diaper dermatitis.

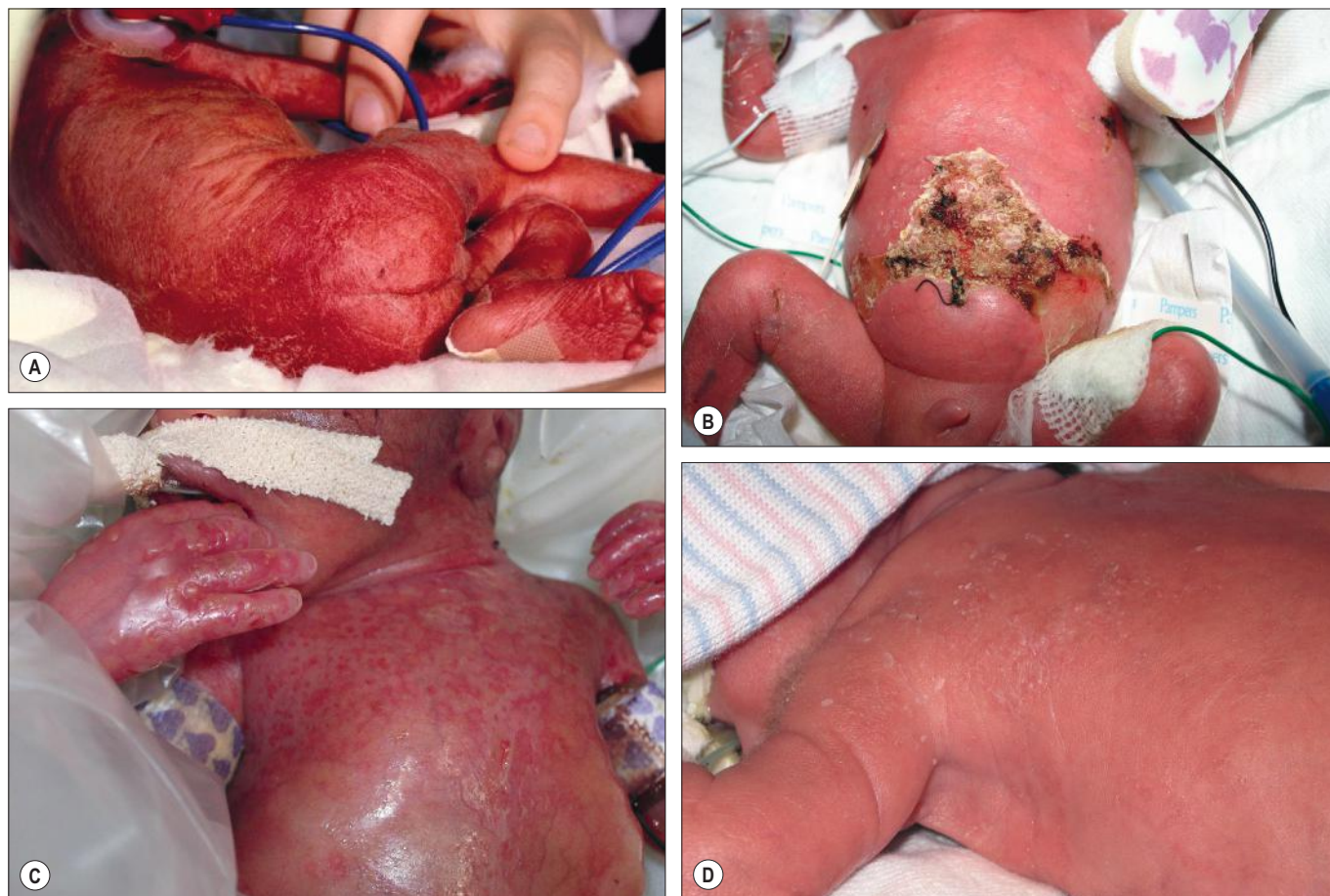


Figure 14.5 (A) Congenital candidiasis in a premature infant. (B,C) Candidiasis with scald-like erythema. (D) Congenital candidiasis. (A: Courtesy of Robert Silverman, MD; D: Courtesy of Ilona Frieden, MD.)



Figure 14.6 White plaques of oral thrush.



Figure 14.7 Candidal diaper dermatitis.

and uninvolved skin (Figs. 14.7, 14.8). Perianal involvement is common. Pustules may be very superficial and rupture easily leaving collarettes of scale. Candidal dermatitis may be seen in 4–6% of term newborns, with the incidence peaking at 3–4 months of age.⁷ Similar bright erythema may be seen in inverse psoriasis. Further differential diagnoses including infectious and noninfectious entities are outlined in Chapter 17.

Candida infections of the nail plate and related structures. Candidal infection of the nail plate and related structures may occur alone or in conjunction with systemic and congenital candidiasis. Candidal paronychia is common in finger-sucking children and presents with erythematous,



Figure 14.9 Nail changes secondary to congenital candidiasis.

edematous and tender nail folds with loss of cuticle. If present for months (chronic paronychia), resulting nail plate dystrophy can be seen distinguishing it from acute bacterial paronychia.

For onychomycosis secondary to *Candida*, finger sucking is a potential predisposing event (Figs. 14.9, 14.10, 14.11). The resultant onychodystrophy may lead to proximal-, distal-, and lateral-subungual, superficial white, or total dystrophic onychomycosis. The latter presents with a crumbling nail and an abnormally thickened nail bed. It is frequently seen in patients with chronic mucocutaneous candidiasis and other immunodeficiency states.²⁶ Tinea unguium, hereditary onychodystrophy, ectodermal dysplasia, epidermolysis bullosa, psoriasis, and acrodermatitis may present with similar nail findings.

Diagnosis

Skin scrapings from pustules or peripheral scale should be examined using KOH solution, Giemsa, Gram, or calcofluor stains. Pseudohyphae and spores may be visualized with direct staining. Satellite pustules are most likely to yield positive results. Cultures from multiple sites, including skin, blood, cerebrospinal fluid, and urine, should be collected if systemic disease is suspected in premature infants or immunocompromised children. Culture yield is inconsistent,⁹ and negative cultures do not rule out systemic disease in the symptomatic infant.⁷ Buffy coat smear microscopy, a rapid bedside test with 100% specificity, can confirm candidemia within 1–2 h. Sensitivity is 62%, compared with 44% for peripheral blood smear examination.²⁷ In some centers, buffy coat culture may yield results faster than whole blood cultures.²⁷ A skin biopsy specimen may reveal a subcorneal pustule with neutrophils, and periodic acid–Schiff (PAS) staining will highlight the organisms. Invasive fungal dermatitis demonstrates invasion and inflammation of the epidermis, and possibly invasion of the dermis. In both neonates and children, *Candida albicans* is the etiologic organism in approximately 50% of candidal infections. As a group, the non-*albicans* species comprise the remaining causes.

Treatment

Localized forms of candidiasis can be treated topically in most term infants and healthy children. For thrush, nystatin solution (100 000 units/mL) is applied to the oral mucosa four times per day for at least 1 week. Resistant thrush may respond to



Figure 14.11 Candidal paronychia.

once-daily oral fluconazole (2–3 mg/kg per day)²⁸ or itraconazole (2 mg/kg per day),²⁹ particularly in immunocompromised children. Oral amphotericin B has been studied for treatment of recurrent thrush.³⁰ Imidazole creams are useful for diaper dermatitis and nail infection. Nystatin, allylamines (including naftifine and terbinafine), or aqueous solutions of 1% gentian violet or 2% eosin are alternatives for localized disease. Inflamed or erosive monilial diaper dermatitis may require a combination of the above with a 1% hydrocortisone cream or ointment and barrier paste containing zinc oxide. Oral nystatin or fluconazole may also be a useful adjunct for the treatment of diaper dermatitis, especially for recurrent disease, concurrent oral candidiasis or persistent cutaneous candidiasis in the setting of prolonged oral antibiotics thereby reducing the load of gastrointestinal *Candida*. Congenital candidiasis in asymptomatic term infants can be treated with topical agents alone. However, for ill and VLBW preterm infants, systemic treatment is recommended.¹⁵

In pediatric patients with invasive candidiasis, successful treatment outcomes are related to the candidal species causing the infection.² *C. parapsilosis* and *C. albicans* have significantly better treatment outcomes than the more virulent *C. glabrata* infections. The drug of choice for systemic antifungal therapy evolves with candidal species, concurrent medical conditions and balance of potential medication side-effects. Early empiric systemic therapy reduces mortality in pediatric patients with candidemia. In ELBW infants, empiric treatment improves survival without associated neurodevelopmental impairment.³¹ Once the candidal species is identified, adjustment of the antifungal agent may be necessary. In neutropenic patients, therapy should be continued for at least 14 days after last positive blood culture.³²

Amphotericin B, a polyene macrolide antibiotic, has been a major therapeutic agent in systemic candidiasis in immunocompromised patients. It is typically utilized in immunocompromised neutropenic patients with prior failed fluconazole prophylaxis or those at high risk of *C. glabrata* or *C. krusei* infections. Less commonly seen in neonates, the potential for nephrotoxicity warrants monitoring of renal function.³³ Hepatotoxicity and bone marrow suppression are also potential side-effects.³⁴ Lipid-associated amphotericin B formulations have less direct renal tubular toxicity and allow delivery of greater



Figure 14.10 Candidal paronychia.

dosages, limits of infusion volume, and less toxicity.³⁵ In addition to use in children, successful treatment of systemic fungal disease with these products has been reported in neonates.³⁶ Both the liposomal and colloidal dispersion forms of amphotericin B were shown to be safe and effective in ELBW infants with candidemia and renal dysfunction.^{33,37} Furthermore, high-dose (5–7 mg/kg per day) liposomal amphotericin B may add a therapeutic advantage with more rapid eradication of infection when used as first-line therapy.³⁸

Systemic fluconazole is commonly used in pediatric invasive candidal infections and has even been used successfully for treatment of systemic candidiasis in neonates.^{39–41} The recommended daily dose is 6 mg/kg per day for patients over 4 weeks of age, with less-frequent dosing for infants with compromised renal function and for those less than 4 weeks old. It is particularly useful in those with *C. albicans* infection and in whom amphotericin B is ineffective or contraindicated.^{33,39} When given in the first trimester of pregnancy, fluconazole has been reported to be teratogenic, leading to multiple malformations.⁴² Resistance to fluconazole can be seen especially in non-albicans *Candida* species (*C. krusei*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*), and also some *C. albicans*.³² Susceptibility testing can be performed to document the utility of these agents.^{32,43}

Oral itraconazole administered at 5 mg/kg per day has been safe and well tolerated in infants and children;^{44,45} however, there are limited reports documenting its use in newborns with candidiasis.⁴⁶ Oral ketoconazole (3–6.5 mg/kg per day) has been largely supplanted by the newer triazoles for candidiasis due to its risk of fulminant hepatitis.⁴⁷

The echinocandins such as caspofungin and micafungin are a relatively new class of pediatric-approved antifungal agents, which irreversibly inhibit 1,3- β -D-glucan synthesis.⁴⁸ These medications are fungicidal against *Candida* spp., including fluconazole-resistant strains, making them especially important for cases of non-albicans candidal infection. In general, the echinocandins have similar efficacy as amphotericin, with fewer adverse side-effects. In one study of caspofungin use in neonates with invasive candidiasis unresponsive to amphotericin B, all cultures cleared after 3–7 days of therapy without adverse events.⁴⁸

Especially in *C. parapsilosis* infections, adjunctive therapy for systemic *Candida* infection includes changing or removing indwelling catheters when feasible.³³ Possibly due to the inability to sterilize the subcutaneous tract of existing lines, exchange of peripherally inserted catheters is associated with a 25-fold increased risk of bloodstream infections.⁴⁹ Placement of new vascular access at a different site is recommended.

Because ELBW infants and immunocompromised children are susceptible to and have a higher mortality risk from systemic *Candida* infections,⁵⁰ prevention of infection by means of fluconazole prophylaxis should receive strong consideration. Potential concerns include unknown short- or long-term risks of fluconazole; uncertainty regarding the group of patients that would benefit most and the optimum dose and duration of therapy; and the potential for increased fluconazole resistance.^{51,52} Fluconazole has been shown to reduce rectal colonization with *Candida*.⁵³ Bertini and colleagues⁵⁴ gave fluconazole 6 mg/kg every 72 h for week 1, then daily for weeks 2–4 in neonates <1500 g with central venous access, and reduced the rate of candidemia from 7.6% to zero. Healy and coworkers⁵⁵ initiated fluconazole prophylaxis in all ELBW infants of <5 days of age and reduced invasive candidiasis-related mortality from

12% to zero. As for dosing, twice-weekly fluconazole (3 mg/kg per dose) in ELBW infants with a central venous catheter or endotracheal tube was as effective as daily prophylaxis in decreasing *Candida* colonization and bloodstream infections.⁵² Meta-analysis of prophylactic fluconazole in this population found both agents to be safe and highly effective in preventing invasive candidiasis.⁵⁶ Although these studies appear promising, larger multicenter studies looking closely at the morbidity and mortality rates from all causes, the emergence of resistant *Candida* strains, and unexpected consequences are still required.⁵²

MALASSEZIA INFECTIONS

Malassezia (previously referred to as '*Pityrosporum*' species) are saprophytic yeasts found on 90% of adults as normal skin flora. Skin colonization of newborns usually occurs in the first 1–3 months of life.^{3,57–59} By means of genetic analysis, the species formerly called *Malassezia furfur* has now been reclassified as *M. furfur* plus at least six other species.⁶⁰ Although *M. furfur* is the most commonly associated species, *M. pachydermatis*, *M. sympodialis*, and *M. globosa* have also been associated with infections.^{59,61,62} Three clinical forms of *Malassezia* infection may present in children: tinea versicolor, cephalic pustulosis, and catheter-associated sepsis without cutaneous lesions.

Skin colonization with *Malassezia* species

Malassezia furfur is the main species responsible for human skin colonization and infection. Other *Malassezia* species, including *M. sympodialis*, *M. globosa*, and *M. pachydermatis* have also been implicated in human disease.^{59,61,62} *Malassezia* colonizes the skin of adults who are usually asymptomatic. Skin colonization begins in infancy, and the prevalence of colonization increases with age.⁵⁸ The most common site of colonization in both infants (>78%) and neonates is the ear.⁵⁸ Ashbee and colleagues⁵⁸ showed that 97.6% of infants (>28 days of age) and 31.8% of neonates were colonized; the mean age of colonization was 14 days.⁵⁸ Risk factors for colonization include gestational age of <28 weeks and length of hospital stay >10 days.⁵⁸ Fungal growth from skin and catheter cultures is not always associated with clinical sepsis.³

Tinea versicolor

Due to the variation of sebum production during life, tinea versicolor (pityriasis versicolor) is less common in infants than in older children, adolescents, and young adults. However, young infants, particularly those less than 6 months of age, can have more sebum production under the influence of the fetal adrenal glands (so-called 'mini-puberty of infancy') and thus are more likely to develop tinea versicolor than older infants or pre-pubertal children. Facial involvement is very typical in affected infants and young children, although lesions may also be seen on the neck and upper trunk.^{63,64} Warm humid weather and immunosuppression induce greater growth of this yeast. A positive family history is variably present. Most commonly caused by *M. globosa* and *M. furfur*, tinea versicolor presents with multiple, 0.3–1 cm oval macules or plaques with fine scaling (Figs. 14.12, 14.13). Relative to normal skin, lesions may be hypopigmented, skin-colored, or hyperpigmented. Wood's light examination highlights the pigmentary changes and may produce a golden fluorescence. Differential diagnoses include pityriasis alba and postinflammatory hypopigmentation and hyperpigmentation.



Figure 14.12 Tinea versicolor.



Figure 14.13 Tinea versicolor.



Figure 14.14 Neonatal cephalic pustulosis.

Neonatal cephalic pustulosis

Neonatal cephalic pustulosis (see [Chapter 7](#)) is a condition that was previously considered to be neonatal acne.^{60,65} During the second or third week of life, multiple, tiny, monomorphic papulopustules on an erythematous base begin on the face, scalp, and neck ([Fig. 14.14](#)). Contrary to classic acne, comedones are not a feature, and follicular accentuation is absent.⁶⁵ Both *M. globosa* and *M. sympodialis* have been reported in association with neonatal cephalic pustulosis.⁵⁹ Higher rates of colonization were associated with increased severity of pustulosis.⁵⁹ Diagnosis is suggested by onset at 1 month of age, cephalic distribution, microscopic findings of yeast forms suggestive of *Malassezia*, exclusion of other pustular eruptions, and response to topical ketoconazole.⁶⁵ The differential diagnosis of this pustular eruption is discussed more extensively in [Chapters 7 and 10](#).

Malassezia sepsis

Malassezia fungemia is seen primarily in premature infants receiving intralipids through intravenous catheters. Skin colonization rates are much higher in premature infants than in full-term newborns, and the pathogenesis of disease probably involves organisms on the skin gaining venous access through indwelling catheters.^{61,66} Although in one study of VLBW infants (<1250 g), skin colonization with *M. furfur* was not predictive of catheter infection or systemic illness, the skin colonization rate was 63%, and positive *M. furfur* blood cultures were common (9.6%) in infants with central venous catheters.³ Clinical presentation ranges from asymptomatic colonization of the indwelling catheter to sepsis and death.^{3,66} Fever, apnea, bradycardia, and thrombocytopenia in the presence of negative routine bacterial cultures suggest fungal disease. Clusters of cases of infantile bronchopneumonia in neonatal units have also been attributed to *M. furfur*.^{66,67}

Diagnosis and treatment of *Malassezia* infections

Malassezia can be identified by KOH preparation or Giemsa stain examination of the fine scales or pus; this will reveal clusters of spherical yeast and associated filaments. *Malassezia* is

differentiated from *Candida* and other yeasts by a broader budding base. *Malassezia furfur* is a lipophilic yeast that requires fatty acid supplementation for growth. Modified Dixon agar or an olive oil overlay on routine fungal media is used for isolation of these fungi from blood specimens.

Cutaneous infections can be treated with an imidazole cream.^{47,65} A high level of suspicion for *Malassezia* sepsis is appropriate in premature infants with clinical signs of sepsis and negative bacterial and viral cultures, especially if intravenous lipid emulsions are being infused through venous catheters. Removal of the catheter and cessation of intravenous lipids, without systemic antifungal therapy, may be sufficient therapy for catheter-associated sepsis. Systemic antifungals may be considered if the infant does not show rapid clinical improvement.⁶⁶

TRICHOSPORONOSIS

Trichosporon asahii (formerly *T. beigeli*), a yeast found in soil and water, causes superficial mycoses in healthy persons (white piedra, onychomycosis, otomycosis).⁶⁸ Invasive disease is possible in immunocompromised hosts and has emerged as a cause of systemic fungal disease especially in very premature infants. Both *T. asahii* and *T. mucoides* have been associated with invasive infection in premature neonates and immunocompromised children.^{68–70} Cutaneous manifestations of trichosporonosis are uncommon, but may include necrotic skin lesions or persistent generalized skin breakdown with serous or purulent drainage and white plaques;⁶⁸ neither erythema nor pustules are present. Unlike adults with trichosporonosis, neonates often have a normal absolute neutrophil count.⁶⁸ Both colonization of central venous lines without evidence of disease and sepsis associated with fungal dissemination are reported in VLBW infants.⁶⁸ Treatment is with a systemic antifungal agent. *Trichosporon* can exhibit tolerance to amphotericin B,^{71,72} and lack of fungicidal activity has been associated with treatment failure and death.⁷¹ Successful treatment of disseminated trichosporonosis with liposomal amphotericin B,⁶⁸ amphotericin plus flucytosine,⁶⁸ fluconazole,⁶⁹ and voriconazole^{70,73} has been reported.

ASPERGILLOSIS

Aspergillus species are ubiquitous saprophytic fungi found in decaying vegetation and are infrequently pathogenic in healthy children.⁷⁴ The conidia can spread through the air, and there are reports of acquisition in immunosuppressed patients following hospital construction work.⁷⁵ *A. fumigatus* is the most common pathogen associated with human infection, followed by *A. flavus* and *A. niger*.^{74–76} The pathogenesis of disease with systemic *Aspergillus* infection involves invasion of blood vessels with subsequent thrombosis and tissue necrosis. Macrophage and neutrophil function is an important immunologic defense mechanism against *Aspergillus* infection.^{74–77} Risk factors for invasive aspergillosis include extreme prematurity, cystic fibrosis, neutropenia or neutrophil incompetence, immunosuppression from severe disease such as malnutrition or bacterial sepsis, and steroid-induced immunosuppression.^{74–77}

Aspergillosis in children presents with a spectrum of diseases, including allergic bronchopulmonary hypersensitization, primary cutaneous aspergillosis, single-system involvement such as pulmonary or gastrointestinal aspergillosis, and disseminated aspergillosis. Mortality rates increase with more invasive disease. There can be overlap in clinical symptoms, and cutaneous lesions can be either primary or secondary to disseminated disease.

Primary cutaneous aspergillosis

Primary cutaneous aspergillosis (PCA) with infection limited to the skin is being reported more frequently in premature infants.^{74,75,77} It is often associated with breaks in normal skin integrity, such as occur with intravenous catheter insertion, or skin erosion or maceration secondary to the use of adhesive tape, monitor leads, or prolonged armboard use.^{74,76} Lesions are often confused with skin trauma or contact dermatitis, and diagnosis can be delayed unless a high level of suspicion is maintained. PCA may begin as a localized zone of erythema, evolving into a dark-red plaque with pustules, and finally a black eschar with a rim of erythema.⁷⁴ Clustered, erythematous papules or pustules, or a necrotic plaque or nodule with an eschar, are characteristic (Fig. 14.15). The differential diagnosis includes ecthyma gangrenosum, zygomycosis, noninfectious vasculitis, and pyoderma gangrenosum.⁷⁴ Histologic evaluation and culture of a biopsy specimen from the affected area can be diagnostic. Microscopically, vesicular surface erosion of a granuloma with infiltrating dichotomously branched (at 45° angles) septate hyphae is apparent. Growth of *Aspergillus* is supportive of a diagnosis, but lack of a positive culture does not rule out disease, especially if hyphal elements are seen on histologic examination.⁷⁵

Systemic aspergillosis

Isolated pulmonary, gastrointestinal, and central nervous system aspergillosis may not be associated with skin findings; however, disseminated aspergillosis can have cutaneous manifestations, and cutaneous aspergillosis may disseminate. A morbilliform eruption that may become pustular is described with systemic aspergillosis.⁷⁵ This presentation often represents embolic phenomena from fungal dissemination. Mortality from systemic aspergillosis in neonates is high compared with that of primary cutaneous aspergillosis (up to 100% vs 27%, respectively).⁷⁵



Figure 14.15 (A) Primary cutaneous aspergillosis. (B) Cutaneous aspergillosis in a premature neonate.

Systemic antifungal therapy is recommended for all forms of systemic aspergillosis. Voriconazole or lipid formulations of amphotericin have been the standard antimicrobial agents prescribed. It is unclear whether complete surgical excision of cutaneous lesions is necessary for cure, but progression of the lesion during therapy may warrant surgical intervention.⁷⁴

Cutaneous zygomycosis (mucormycosis, phycomycosis)

Zygomycosis is the term for infection caused by fungi in the Zygomycetes class. There are six fungal genera that cause disease in humans: *Rhizopus*, *Cunninghamella*, *Mucor*, *Rhizomucor*, *Saksenea*, and *Absidia*.⁷⁸ These fungi are found in soil, decaying food, and other organic matter. Although infections may follow ingestion or inhalation of spores, direct inoculation into skin is the cause of primary cutaneous zygomycosis. It is seen predominantly in premature infants, as well as those who are immunocompromised from immunosuppressive drugs or underlying disease.^{78,79} Due to the selective pressure of more frequent use of newer (non-amphotericin) antifungal medications, some centers have reported an increase in invasive



Figure 14.16 Cutaneous *Rhizopus*: pustules developed under tape adhesive.

zygomycosis.⁸⁰ Similar to aspergillosis, zygomycosis can involve the skin alone (primary cutaneous) or may involve other organ systems, including the gastrointestinal, pulmonary, and central nervous systems. Skin lesions may represent dissemination, or primary cutaneous infection may disseminate. Zygomycosis in immunocompetent hosts includes cutaneous zygomycosis and sinusitis. The cutaneous lesions may present as pustules with or without discrete erythematous cellulitis, and may develop a sharply defined, black, necrotic plaque producing a pathognomonic black pus (Fig. 14.16).⁷⁹

In a review of 31 cases of neonatal zygomycosis, 22 were in premature infants, of which 12 had skin as the initial site of infection.⁷⁸ Reports include an association with contaminated dressings and tongue depressors used as splints for intravenous and arterial cannulation sites.^{78,79,81} The Centers for Disease Control and Prevention (CDC) recommends that skin dressings be treated with cobalt irradiation as a preventive measure.⁷⁹

Diagnosis is made by tissue biopsy and culture. Histologic examination shows large, nonseptate hyphae with right-angled branching.⁸² The fungus invades downward into tissue and blood vessels, frequently leading to thrombosis with dermal edema and minimal inflammatory infiltrate.⁸² Vascular invasion results in cutaneous ischemia and necrosis.^{78,82}

Zygomycosis is treated with intravenous amphotericin B. As with aspergillosis, lipid formulations of amphotericin B can be used to deliver higher concentrations of drug, and other agents such as rifampin may be of use for antimicrobial synergy.^{78,83} In vitro data reveal resistance to azoles (except for *Absidia*), flucytosine, and naftifine.⁸⁴ Although one successful case of medical treatment alone is reported,⁷⁹ surgical debridement is often imperative in the treatment of cutaneous zygomycosis, and wide excision with clear margins of involved tissue is recommended.^{78,83} Overall mortality in invasive zygomycosis is 64% in neonates and 56% in children.⁸⁵

DERMATOPHYTOSIS

Dermatophytes are common fungal pathogens responsible for the cutaneous infection known as tinea. Clinical conditions



Figure 14.17 Annular, scaling plaques on this 2-week-old infant due to *T. tonsurans* infection.

are named according to the affected anatomic location: tinea capitis (scalp), tinea faciei (face), tinea corporis (body), tinea diaper dermatitis (diaper area), tinea unguium (nails), tinea cruris (groin) and tinea pedis (feet). Dermatophytosis may be acquired from infected caregivers, infected animals, or via fomites e.g. combs and brushes. Dermatophyte invasion of the stratum corneum is mediated by keratinase and other proteases.⁸⁶ Cell-mediated immunity and evidence of a delayed-type hypersensitivity response are important in host resistance.⁸⁶

In North America, dermatophyte infections in children are most often due to *Trichophyton tonsurans* and *Microsporum canis*.^{87–90} In Europe, *M. canis* is the most common, followed by *T. mentagrophytes*.^{90–93} The most common cause of tinea capitis in North America is *Trichophyton tonsurans*, which may also cause tinea faciei and corporis secondary to cutaneous spread. Fungal invasion in tinea capitis extends to the hair follicle, where infection may be either within the hair shaft (endothrix) or on the surface of the hair shaft (ectothrix). Neonatal tinea capitis has been reported with other fungal species, including *T. rubrum*, *T. violaceum*, and *T. erinacei*.^{90,94,95} Tinea diaper dermatitis is primarily due to *T. rubrum* and *Epidermophyton floccosum*.⁹⁶ Tinea unguium in childhood has been caused by *T. mentagrophytes* and *T. rubrum*.⁹⁷

Clinical findings

Dermatophyte infections in infants occur most commonly on the exposed scalp and face (Fig. 14.17).^{3,87–89,91–95} Tinea capitis often presents as erythematous, scaling areas with partial alopecia.^{90,93} Clinical manifestations vary from noninflammatory ‘black dot’ alopecia to a scaling, seborrheic dermatitis-like eruption without obvious hair loss (Fig. 14.18).^{90–92} Pustules may be present.⁸⁷ Kerions can be seen in conjunction with tinea capitis.⁸⁷ Kerions consist of pustules, nodules, and crusting, with underlying boggy scalp tissue. The inflammatory nature mimics a bacterial infection and often leads to unsuccessful therapy



Figure 14.18 Infant with tinea capitis.

with antibacterial agents. Tinea capitis associated with kerion formation has been reported in a neonate.⁸⁷ Posterior cervical lymphadenopathy is usually present. The kerion represents a delayed hypersensitivity reaction to the infection and may occur in 2% of patients with tinea capitis.⁹⁸ Cultures from kerions can be negative in 40% of cases.⁹⁸

Tinea infection on other parts of the body usually presents as annular plaques with superficial scaling and/or tiny pustules.^{89,94,95} These may be mistaken for dermatitis; facial tinea may mimic neonatal lupus. Cases of tinea faciei and tinea corporis have been reported in neonates.^{88,94,99} Cases of resistant diaper dermatitis in infants as a result of dermatophytes have been described.⁹⁶ In tinea diaper dermatitis, the presence of annular or arcuate plaques with a scaling peripheral border is a clue to the diagnosis (Fig. 14.19).

Tinea pedis was once thought to be rare in young infants. While certainly not as common as in teens or adults, many cases have been reported. A major risk factor is the presence of tinea pedis or onychomycosis in one or more family members. The clinical presentations are similar to those in older patients including web-space scaling as well as scaling of the forefoot. Because of low level of suspicion, many affected children are misdiagnosed as having a dermatitis.^{100,101}

Onychomycosis, fungal infection of the nail, can be caused by dermatophytes, nondermatophyte molds, and *Candida*. Tinea unguium, caused by dermatophytes, is uncommon in prepubertal children but is occasionally seen.⁹⁷ *Candida* onychomycosis is a relatively common finding in neonates with congenital cutaneous candidiasis.^{14,17} Nails may have superficial white opaque patches, or yellowish discoloration with subungual hyperkeratosis. Hereditary onychodystrophy, acquired trachyonychia, psoriasis, lichen planus, and trauma may cause similar findings.

Diagnosis

Diagnosis of dermatophytosis can be confirmed by several tests. A Wood's light examination may have limited usefulness in the diagnosis of tinea capitis; positive fluorescence is seen in ectothrix hair infections, but is absent in the more common endothrix infections such as those caused by *Trichophyton*. All suspected tinea infections should be confirmed by culture, or



Figure 14.19 Dermatophyte diaper dermatitis (note scaling edge).

lesional scale or hair microscopically examined under 10% potassium hydroxide (KOH) solution or alternative stains (see Chapter 6). Although KOH preparations may demonstrate spores and hyphae, false-negative examinations are common. Scrapings of scales, brush or cotton-tipped applicator swabbings of the affected skin, or collections of hair are cultured on fungal media. Dermatophytes are slow growing and may take up to 1 month to grow in culture, although common pathogens generally grow within 2 weeks. Skin biopsy, although rarely necessary for diagnosis, may reveal hyperkeratosis with parakeratosis and a mixed inflammatory perivascular dermal infiltrate. Staining with periodic acid–Schiff (PAS) or Grocott–Gomori methenamine silver nitrate reveals fungal elements in the stratum corneum and possibly the hair follicle.⁴⁷

Treatment

Treatment of tinea capitis usually requires systemic antifungal therapy. Griseofulvin has been used for decades and successful safe treatment even in neonates has been reported.^{87,90,93} Griseofulvin suspension doses of 20–25 mg/kg per day for 8 weeks may be needed.^{87,90,93} Ultramicronized griseofulvin is better-absorbed allowing for reduced dosages at 15–20 mg/kg per day. Fluconazole (6 mg/kg per day) may also be effective.¹⁰² Terbinafine is fungicidal and may require shorter treatment durations. Experience with terbinafine in neonates is limited, but has been studied in children as young as 2 years of age with good tolerance demonstrated. Terbinafine, dosed at 5–8 mg/kg daily for 6 weeks, has been shown to have efficacy against both *Trichophyton* and *Microsporum* species in pediatric cases of tinea capitis.^{103,104} Although topical therapy alone was successful in treatment of infants (mostly preterm infants with *M. canis* tinea capitis) during a nursery outbreak,⁹³ it is not generally recommended for tinea capitis.^{88,93} A well-reported complication of tinea capitis is auto-eczematization ('id' reaction) which occurs in a minority of patients, typically those with either severe or long-standing disease. This reaction typically manifests as intensely pruritic monomorphic and symmetrically distributed papules on the hair line, ears, and upper torso and proximal extremities. Onset is usually just after the initiation of systemic treatment of tinea capitis, however it does not represent true allergy to the oral antifungal medication.

Tinea faciei, corporis, and pedis can be successfully treated with topical applications of azoles such as clotrimazole, econazole, and miconazole. Ciclopirox, as well as allylamines such as terbinafine or naftifine and amorolfine, may also be used.^{105,106} If persistent, systemic griseofulvin or fluconazole for a period of 4–8 weeks may be required.^{102,107} Majocchi's granuloma is a follicular dermatophyte infection on non-scalp locations. These granulomatous dermatophyte infections typically occur when the initial superficial fungal infection is mis-treated with topical steroids allowing the dermatophyte to invade hair follicles. Systemic treatment is necessary to eradicate this deeper dermatophyte infection. It is important to identify the potential source of the fungal infection in family members. The prognosis for dermatophyte infections is excellent.

Ectoparasitic infestations

Mites, lice, bed bugs, flea larvae, protozoa, and helminth worms cause a variety of cutaneous lesions.⁴⁷ Mites are classified in the order *Acari*, class of arthropods *Arachnida*. The prototype is scabies, which is the most common parasitic infection in humans. Flea larvae (myiasis) and other mites (demodicidosis) can also cause disease in children.

SCABIES

Introduction

Scabies is a common ectoparasitic infestation caused by the mite *Sarcoptes scabiei* ssp. *hominis*. Initial infestation by scabies may be asymptomatic. A primary symptom of scabies is generalized pruritus, which intensifies at night. Infants, however, may not manifest symptoms despite extensive infection. Pruritus in a neonate unable to scratch may present as irritability, insomnia, and poor feeding. Congenital scabies is not seen, but infestation can develop in very young infants.^{108,109}

Cutaneous findings

Skin findings include a generalized erythematous vesiculopapular eruption, with lesions commonly concentrated on the axillae, neck, palms, soles, and sometimes the head (in young infants, Fig. 14.20). In older children and adults, the head and neck are usually spared. A burrow is the pathognomonic sign of scabies. Burrows appear as a small thin line with a tiny black dot at one end, indicating the location of the female mite. They are found primarily on the hands, flexural aspect of the wrists (Fig. 14.21), and medial or lateral aspects of the



Figure 14.20 (A–D) Scabies. (C: Courtesy of Angela Hernandez-Martin, MD.)



Figure 14.21 Scabies on the wrist. (Courtesy of Angela Hernandez-Martin, MD.)



Figure 14.22 Scabies. *Sarcoptes scabiei* mite and eggs.

feet; visualization may be difficult because of secondary eczematous changes.

In infants, vesicles and pustules are characteristically found on the palms and soles. Nodules representing a hypersensitivity reaction may also appear, primarily in intertriginous areas, during active infection, and persist for some time after scabies has been successfully treated. Recurrent vesicular lesions similar to scabetic nodules may be manifestations of ongoing hypersensitivity response to the initial infestation.

A form of infantile scabies (scabies incognito) clinically resembling crusted scabies is associated with prior topical corticosteroid therapy.¹⁰⁹ In addition to the generalized eruption, crusted and hyperkeratotic lesions on the palms and soles are described.¹¹⁰ Unlike classic crusted scabies in adults, which is characterized by intense infestation by *Sarcoptes* mites, these infants lacked subungual hyperkeratosis and high mite counts.¹¹⁰ There has also been a report in immunosuppressed children of a unique form of scabies consisting of fine scaling and minimal to absent pruritus, mimicking seborrheic dermatitis.¹¹¹

Etiology and pathogenesis

The scabies mite is an obligate human ectoparasite unable to survive more than a few days without a host.¹⁰⁸ The microscopic adult female mite has eight legs and measures 400 μm . Throughout its life span of up to 30 days, the mite burrows into the stratum corneum, laying up to three eggs per day. Larvae hatch in 3–4 days, and mature into adult mites within 10–14 days.¹⁰⁸ Although only a few mites are present, hundreds of skin lesions may develop owing to hypersensitivity.¹⁰⁸

Diagnosis

Diagnosis is based on the clinical findings, as well as a history of contact with persons having a similar pruritic eruption. Definitive diagnosis is based on microscopic visualization of scrapings from a burrow or papule, demonstrating the mite, eggs, or scybala (feces) (Fig. 14.22) (see Chapter 6). Skin biopsy is rarely necessary. Histopathologic examination shows a mixed dermal inflammatory infiltrate with eosinophils and epidermal spongiosis. The mites, ova, and nymphs may also be seen.

Treatment

The treatment of choice for scabies is permethrin 5% cream. It is approved for use in infants as young as 2 months old, with one report of safety and efficacy in a 23-day-old infant.¹⁰⁸ Permethrin is a neurotoxin that causes paralysis and death of ectoparasites; it has low potential for toxicity in humans, and there is no evidence of resistance to date.¹⁰⁴ Efficacy is superior to that of lindane, crotamiton, benzyl benzoate, and sulfur.¹⁰⁴ Permethrin applied to the entire body surface, including the scalp, and left on for 8–12 h is 89–92% effective.¹⁰⁸ Reapplication 1 week later is advisable. Critical to success is the simultaneous treatment of all family members and close contacts, even if asymptomatic. In households in which not all members are treated, it is not uncommon for the return of lesions in initially improved patients. Whereas adults are treated from the neck down, children under 2 years of age should have the head treated as well. In addition, bedding and clothing of patients and all contacts should be washed the following day in hot water for at least 5 min, or dry cleaned. Antihistamines such as hydroxyzine (2 mg/kg per day in divided doses every 6–8 h) and a corticosteroid ointment such as triamcinolone 0.1% may help control the residual pruritus and eczematous dermatitis that can persist for several weeks following successful eradication of the parasite. Ivermectin, an avermectin with antiparasitic and anti-nematode properties, has been used orally in cases of refractory scabies,¹¹² but it is not recommended for use in patients under 15 kg body weight.

PEDICULOSIS CAPITIS (HEAD LICE)

Introduction

Head lice infestation is common in the pediatric population, affecting 1–10% of school-aged children.¹¹³ The causative insect *Pediculus humanus* var. *capitis* is spread by close person-to-person contact and by fomites (combs, hats, pillows, etc.).¹¹⁴

Cutaneous findings

Although head lice are less commonly seen in infants than in school-aged children, infants are at risk of infestation through



Figure 14.23 *Pediculus humanus* var. *capitis*

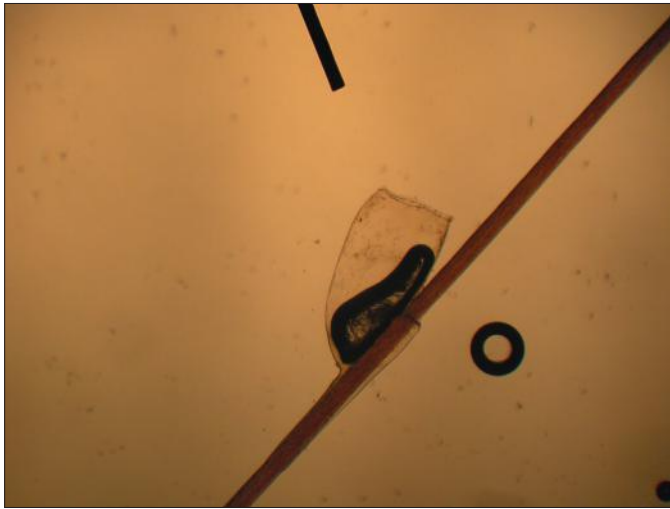


Figure 14.24 Head lice nit.

close physical contact and fomite sharing with older siblings. The most common presenting symptom is scalp pruritus.

Etiology

Adult lice are 1–2 mm long or approximately the size of a sesame seed (Fig. 14.23). They lay eggs on the hair shaft in firmly adherent casings called ‘nits’ usually within 2 mm of the scalp (Fig. 14.24).¹¹⁴

Diagnosis

Visualization of lice attached to the hair shaft is diagnostic and they are most commonly found behind the ears and at the nape of the neck.¹¹⁴

Treatment

Traditional lice treatments include permethrin 1% rinse (available as Rid® and Nix® in the USA without a prescription) and malathion 0.5% lotion (requires a prescription). Resistance to pyrethroids is unfortunately becoming widespread and treatment requires several repeat applications due to poor ovicidal activity of these compounds.¹¹⁵ Malathion has efficacy data in patients as young as 2 years of age and has been shown to be superior to permethrin in ovicidal activity.¹¹⁶ While high alcohol content of the vehicle requires caution around an open flame, there are no verified reports of bodily harm due to burns when using this product.¹¹⁶

Although it was a first-line treatment in the past, lindane (gamma-benzene-hexachloride) is now rarely used due to significant risk of neurotoxicity (seizure, headache, dizziness, and paresthesia) and other adverse events, especially in pediatric populations.¹¹⁷ Resistance to both permethrin and malathion has been reported¹¹⁸ and new therapies are available. Spinosad 0.9% topical solution is approved for use in children over four years of age.¹¹⁹ Spinosad is ovicidal, killing both lice and nits, and has been shown to be superior to permethrin 1% cream rinse.¹²⁰ Ivermectin 0.5% lotion (Sklice®) is also recently approved and has safety data in children as young as 6 months of age.

Physical treatment modalities such as hot air directed at the scalp to desiccate the insect¹²¹ and suffocation therapy (application of olive oil, mayonnaise, etc. to the scalp) have also been shown to be effective treatments.^{122,123} In children over 2 years of age, oral ivermectin (at a dose of 400 µg/kg of body weight) has been shown to be effective for malathion-resistant head lice cases as well.¹²⁴ Most treatments are repeated 7–10 days after the initial application to ensure eradication of any lice hatching from eggs that survived the first round of therapy. Use of a nit comb is also helpful to physically remove potentially resistant eggs from the hair shaft. Nit combs are helpful as an adjunct but are insufficient as solo therapy.¹²⁵ All close contacts should be treated simultaneously as lice infestation can be asymptomatic.¹²⁶ Lice can survive off the human host for up to 55 h and nits can survive up to 10 days. Therefore, measures to treat the environment are also recommended. All washable fomites (clothes, bedding, etc.) should be laundered in hot water and dried on high heat for at least 40 min.¹²⁷ Non-launderable items should be placed in a bag for 3 weeks or dry-cleaned. Fumigation with pesticides is not recommended.

ENTEROBIASIS (PINWORMS)

Enterobiasis is due to infestation with the nematode *Enterobius vermicularis*. Infestation is most common in school-aged children but is easily transmitted to household contacts and may be seen in younger infant siblings. Although most infestations are asymptomatic, it may present as nocturnal perianal pruritus. The pruritus is caused when the gravid female pinworm deposits her eggs in the mucosa of the perianal area at night-time. Traditional diagnosis is by the application of clear cellophane tape to the perianal area upon waking followed by microscopic examination of the tape for the presence of eggs. Treatment with antihelminths such as mebendazole, albendazole or pyrantel should be prescribed for the patient and all close contacts. Treatment should be repeated in 1 week.

CUTANEOUS LARVA MIGRANS

Cutaneous larva migrans, also called ‘creeping eruption,’ is due to larvae of the dog and cat hookworm (*Ancylostoma caninum* and *Ancylostoma braziliensis*) burrowing in human epidermis. Humans are accidental hosts and the hookworm is unable to complete its normal life cycle. Instead, the larvae are confined to the epidermis and migrate aimlessly for 1–2 months until they die. They cause significant pruritus and linear erythematous serpiginous plaques on the skin that lengthen up to 1–2 mm/day. The infestation responds to treatment with traditional oral antihelmintic medications (albendazole, mebendazole, ivermectin, etc.).

DEMODICIDOSIS

Demodicidosis presents as perioral dermatitis, pustular folliculitis, and blepharitis.¹²⁸ Pruritic erythematous papules, pustules, nodules, and scaling occur primarily on the face, most commonly on the dorsum of the nose.¹²⁹ *Demodex folliculorum* and *D. brevis* are human ectoparasites that are normal inhabitants of the pilosebaceous ducts and glands. *D. canis* causes mange in animals. The role of the mite *Demodex* in human cutaneous disease is controversial.¹²⁸ To date, the youngest reported case is

that of a 10-month-old infant.¹²⁷ Demodicidosis is found mainly in immunosuppressed children,^{128,130} although disease in healthy hosts has been described.¹²⁹ A well-described scenario in children occurs in those with acute lymphocytic leukemia on maintenance chemotherapy. Mites may be seen when skin scrapings are examined using KOH or when a skin biopsy is performed. A dramatic response may be seen within 2–3 weeks after the application of 5% permethrin cream.¹²⁸ Topical metronidazole and oral erythromycin help decrease the numbers of mites and may offer additional benefit.^{128,129}

MYIASIS

Myiasis is a parasitic infestation of dipterous larvae in mammals, found worldwide but primarily in the tropics and subtropics.¹³¹ Cutaneous myiasis may occur in pre-existing wounds or present as a furuncle. Passage of maggots, discharge, a foul odor, and pain may be reported.^{132,133} Myiasis is classified clinically according to the body site affected, as cutaneous, nasopharyngeal, ocular, aural, intestinal, or genital. There have been reports of myiasis in neonates and infants chiefly in rural settings,¹³² although cases have also been reported in urban centers and neonatal intensive care units.¹³³ The diagnosis is made clinically and confirmed by identification of larvae, which can be preserved in 80% ethanol. Treatment involves extraction of the

larvae by irrigation, manipulation, or ideally with surgery followed by debridement, cleansing, and possible primary suture closure.¹³¹

Parasitic infections

Parasitic infections with cutaneous manifestations are more commonly seen in developing countries. Table 14.1 presents a summary of cutaneous diseases due to parasites. *Toxoplasma* are autonomous, single-cell organisms that are acquired in utero more frequently than postnatally. Cutaneous manifestations of helminth worms are discussed minimally here, but are treated in depth by Stein.⁴⁷

TOXOPLASMOSIS

Toxoplasmosis is caused by the intracellular protozoan *Toxoplasma gondii*.^{134–136} Infection commonly occurs through consumption of undercooked meats containing *Toxoplasma* cysts or oocysts excreted by cats.^{136,137} Toxoplasmosis may be acquired congenitally or postnatally. Severity of fetal disease varies inversely with gestational age at the time of infection. Thus early infection more likely leads to fetal death or severe neurologic and ophthalmologic disease.¹³⁷ Most newborns infected in the second or third trimester have mild or subclinical

TABLE 14.1 Parasitic cutaneous infections in neonates

Parasite	Name	Source	Clinical findings	Therapy
Mite				
<i>Sarcoptes scabiei</i> ssp. <i>hominis</i>	Scabies	Human	Classic burrow; vesicles on palms and soles; nodules, papules, and pustules on face and extensors	Permethrin 5% cream or lotion, including scalp, Tx contacts
<i>Demodex folliculorum</i>	Demodicidosis	Human saprophyte	Papules and pustules on face and extensors	Permethrin 5% cream or lotion
Protozoa				
<i>Toxoplasma gondii</i>	Toxoplasmosis	Cats	Acquired: variable Congenital: chorioretinitis, hydrocephalus, intracranial calcifications, ± petechial rash	Pyrimethamine and sulfonamide, or spiramycin, or trimethoprim-sulfamethoxazole
<i>Entamoeba histolytica</i>	Amebiasis	Humans 10% worldwide GI tract colonized	Ulcer, draining sinus, vegetative plaque in the inguinal, perineal area, abdomen	Metronidazole and iodoquinol or paromomycin
<i>Leishmania major</i> , <i>L. tropica</i> , <i>L. aethiopica</i>	Cutaneous leishmaniasis (Old World)	Female sandfly, mammal reservoir	Single or multiple papules and nodules ± ulcer resolving to leave scars	Sodium stibogluconate, meglumine antimoniate ± allopurinol, ketoconazole, itraconazole, amphotericin B, cryotherapy, heat
<i>L. mexicana</i> , <i>L. braziliensis</i>	Cutaneous leishmaniasis (New World)			
<i>L. braziliensis</i>	Mucocutaneous leishmaniasis		Destructive oral, nasopharyngeal lesions	
<i>L. donovani</i>	Visceral leishmaniasis (Kala-azar)		Gray skin color, nodules	
Myiasis: (fly larvae) order <i>Diptera</i>	Myiasis	Flies, gnats, mosquitos	Furuncle or infested ulcer	Surgical removal
Helminths: Platyhelminthes (tapeworms)	Rare in newborns			
Trematodes				
Cestodes				

manifestations. In at least 40% of cases, the infection is discovered late, manifesting as chorioretinitis, visual impairment, and neurologic sequelae.^{135,137} Risk of fetal infection is estimated to be <1–19.6/10 000 live births worldwide, varying with geographic location.¹³⁸

Congenital toxoplasmosis has no specific cutaneous manifestations,^{134–136} but petechial and nonpetechial rashes were seen in, respectively, 17% and 14% of affected infants.¹³⁹ Deep blue-red papules and macules and nonspecific exanthems, both with involvement of the palms and soles, and a calcifying dermatitis have been described in affected neonates.¹³⁶ Neurologic sequelae such as seizures, hydrocephalus, microcephaly, and neuropsychomotor developmental delay are the main clinical manifestations.¹³⁷ Intracranial calcifications and increased CSF protein may be seen. Eye abnormalities include chorioretinitis (95%), microphthalmia, cataracts, and retinal detachment. The most common clinical presentation of eye involvement is strabismus, seen in 49% of affected infants.¹³⁷ Neonatal disease may include systemic findings of hepatosplenomegaly, lymphadenopathy, hyperbilirubinemia, and thrombocytopenia. The prognosis of congenital toxoplasmosis has improved with therapy; however, many cases are not recognized in the newborn period.¹³⁴

Postnatally acquired toxoplasmosis is asymptomatic in the majority of patients, but disease in immunocompromised hosts can be serious. Cutaneous manifestations are variable and include macular, papular, pustular, or vesiculobullous eruptions.¹³⁶ The eruption may be hemorrhagic and may resemble roseola or erythema multiforme.⁴⁷ Lymphadenopathy and hepatosplenomegaly may accompany these eruptions.

The diagnosis of toxoplasmosis is based on isolation of the organism, characteristic histopathology of lymphadenitis, detection of *Toxoplasma* antigens in tissues and body fluids, and detection of *Toxoplasma* nucleic acid by PCR. The most commonly used diagnostic tool is serology. Both the enzyme-linked immunosorbent assay (ELISA) and immunosorbent agglutination assay (ISAGA) are useful tests.¹³⁵ The Sabin–Feldman dye test entails the uptake of methylene blue by *Toxoplasma* trophozoites lysed in the presence of specific antibody and complement. It is very specific but only available through reference laboratories.¹³⁵ PCR testing of amniotic fluid replaced cordocentesis for the prenatal diagnosis of fetal infection.¹⁴⁰

Symptomatic acquired or congenital toxoplasmosis should be treated with pyrimethamine, sulfadiazine, and folinic acid.¹³⁵ Treatment should be continued for at least 1 year.

LEISHMANIASIS

Leishmaniasis is a parasitic infection due to *Leishmania* species (family Trypanosomatidae). There are 400 000 new cases each year in Asia, Africa, the Mediterranean, and the Americas. The flagellated, extracellular promastigote is transmitted by female phlebotomine sandflies to animal reservoirs, including rodents and dogs.¹⁴¹ There it becomes an obligate intracellular amastigote. Reports of infants with leishmaniasis living in non-endemic areas emphasize the need to consider this diagnosis when unusual skin lesions are present.^{141–144} Leishmaniasis is classified into the following categories: visceral (*L. donovani*, *L. infantum*), mucocutaneous (*L. braziliensis*), Old World cutaneous (*L. major*, *L. tropica*, *L. aethiopica*), and New World cutaneous (*L. mexicana*, *L. braziliensis*) (Table 14.1).¹⁴⁵



Figure 14.25 Cutaneous leishmaniasis. (Courtesy of Antonio Torrelo, MD.)

Visceral leishmaniasis due to *L. donovani* presents with fever, wasting of the face and extremities, hepatosplenomegaly, ascites, pancytopenia, and earth-gray skin pigmentation on the temples, perioral area, hands, and feet.¹⁴¹ There may be a papular lesion seen early at the site of the sandfly bite. Mucocutaneous leishmaniasis due to *L. braziliensis* invades the midface, nose, and upper respiratory tract. A sporotrichoid lymphatic form has been described with *L. braziliensis* and *L. major*.

In countries where leishmaniasis is prevalent, infants and children are frequently affected by cutaneous leishmaniasis. The initial lesion is an erythematous papule derived from an insect bite that evolves to form a relatively painless crusted ulcer.¹⁴¹ It is typically on an exposed site (primarily on the face and hands) (Fig. 14.25), paired or clustered, with a volcanic or iceberg appearance, and oriented to the skin creases. Satellite papules or nodules may be present with surrounding erythema.¹⁴⁴ Secondary bacterial infection is common. The lesions generally heal spontaneously in 3–12 months, although they may also evolve into chronic, treatment-resistant forms that are localized, lupoid, or disseminated.

Diagnosis is based on smears or skin biopsy specimens that permit visualization of the amastigote, culture, or animal inoculation that produces characteristic lesions.¹⁴¹ The leishmanin skin test evaluates the degree of induration after an intradermal injection of antigen. Positive findings are seen 1–3 months after the initial lesion in cutaneous leishmaniasis. Serologic studies are most valuable in visceral leishmaniasis.¹⁴¹

Although visceral leishmaniasis is usually fatal if untreated, spontaneous resolution is the rule in cutaneous forms of the disease. Indications for treatment include lesions that are early, multiple, mucosal, or in cosmetically sensitive sites. Disseminated disease in an immunodeficient host also warrants treatment. If treatment is needed, there is no single ideal drug. Primary treatment is with pentavalent antimonials such as intramuscular or intravenous sodium stibogluconate (10–20 mg/kg per day) or meglumine antimonate (not available in the USA).¹⁴⁶ Ketoconazole and amphotericin B may also be effective, and temperature-sensitive *Leishmania* may respond to cryotherapy or heat.¹²¹



Figure 14.26 (A–D) Insect bites.

Arthropod bites and stings

Arthropod bites and stings may cause a variety of skin lesions, as well as be vectors for disease. Erythematous, urticarial papules and pustules with a central punctum can be seen, most commonly on exposed surfaces (Fig. 14.26). Vesicular lesions may be a manifestation of a hypersensitivity response and not indicative of bacterial infection, particularly in infants and young children. These pink, raised lesions are typically arranged in groups. Persistence of lesions for weeks to months (papular urticaria) is rarely seen in the first year of life.¹⁴⁷ Specific lesions and subsequent diseases are outlined in Table 14.2.

Skin lesions are caused by four of the nine classes of arthropod: Insecta, Chilopoda, Diplopoda, and Arachnida.¹⁴⁸ Although the terms bite and sting are often used interchangeably, in the strict sense, a 'bite' involves venom injected via structures of the mouth, such as fangs or mandibles, whereas a 'sting' connotes the injection of venom via a tapered posterior structure called the sting.¹⁴⁹ Secondary bacterial infection must be considered in infants with bites and stings. The presence of fever and wound drainage is suggestive of infection and may warrant antibiotic therapy.

PAPULAR URTICARIA

Brief introduction

Papular urticaria is a hypersensitivity reaction to a wide variety of insect bites (bed bugs, flea, mosquitoes, flies, mites, chiggers, etc.) seen most frequently in children age 2–10 years.

Cutaneous findings

Papular urticaria is characterized by chronic or recurring eruptions of multiple pruritic papules, vesicles or wheals that occur on exposed areas of the body such as the arms and legs (Fig. 14.27). In the case of bed bugs and other walking insects, bites are characterized by linear arrangement of erythematous papules and are often found in groups of three ('breakfast, lunch and dinner' sign). It can be extremely resistant to therapy and individual lesions can persist for months. New insect bites can cause old lesions to become inflamed again.

Diagnosis

Diagnosis is based on the cutaneous findings and a history of exposure to insects. In the case of bed bugs, a search of mattress

TABLE
14.2

Arthropod bites and stings

Class	Order	Source	Lesions	Treatment	Disease
Insecta (three pairs of legs)	Anoplura	Lice: <i>Pediculus humanus</i> , <i>Phthirus pubis</i>	Nits, pruritic bites, maculae caeruleae	5% permethrin; Tx fomites	
	Coleoptera	Beetles	'Kissing' or touching blisters and dermatitis	Topical corticosteroid, systemic antihistamine	Secondary bacterial infection
	Diptera	Mosquitos	Pruritic papules	Topical corticosteroid, systemic antihistamine	Vector for: Encephalitis Malaria Yellow fever Dengue fever Filariasis
		Flies (bloodsucking)	Pruritic, painful papules	Topical corticosteroid, systemic antihistamine	
		Tabanae: horseflies, deerflies, etc.	± angioedema	Topical corticosteroid, systemic antihistamine	Vector for: Tularemia
		Simuliidae: black flies	± malaise		
		Midges; sandflies			
	Hemiptera	Cimicidae (bed bugs)	Pruritic papules	Topical corticosteroid, systemic antihistamine	Vector for: <i>Trypanosoma cruzi</i>
		Reduviidae (kissing bugs)	Painful bites	Topical corticosteroid, systemic antihistamine	
	Hymenoptera	Apidae (bees)	Urticarial papule	Quick removal of stinger, s.c. epinephrine, corticosteroid, antihistamine	
		Vespidae (wasps, hornets)	Angioedema		
		Formicoidea (ants)			
	Lepidoptera	Caterpillars	Urticarial linear papules	Topical corticosteroid, systemic antihistamine	
		Moths			
Arachnida (four pairs of legs)	Siphonaptera	Fleas: Pulicidae (human, cat, dog, bird)	Grouped papules	Topical corticosteroid, systemic antihistamine	Vector for: Plague Typhus
		Sarcopsyllidae (sandfleas)	Necrotic abscess	Topical corticosteroid, systemic antihistamine	
		Ticks: Argasidae, Ixodidae	Papule, granuloma	Remove tick	Vector for: Lyme disease Rocky Mountain spotted fever Colorado tick fever Tularemia
					Vector for: Rickettsial-pox
		Mites: Follicle, food, fowl, grain, harvest (chigger), murine, scabies	Pruritic papules	Topical corticosteroid, systemic antihistamine	
	Araneae	Spiders	Painful bite ± necrosis ± systemic reaction	Ice, elevation, antihistamine, analgesic	
	Scorpiones	Scorpions			
		Centipedes			
		Millipedes			
Chilopoda					
Diplopoda					

s.c., subcutaneous.



Figure 14.27 (A,B) Papular urticaria from mosquito bites.

Continued



Figure 14.27, cont'd (C-F) Papular urticaria from mosquito bites (C), and bed bugs (D-F). (Courtesy of Ilona Frieden, MD.)

seams or rough cracks and crevices can reveal areas where the insects remain hidden during the daytime. Asking about pets and possible flea exposure is also a helpful part of the history. For mosquito exposure, the caregivers will often report a history of the rash flaring during the times of the year that mosquitoes are most active.

Etiology

The cause of papular urticaria is widely varied and often depends upon the region in which it occurs.^{150,151} In the south-east, it is most commonly caused by mosquitoes and tends to flare in the summer months. In the western USA, however, fleas and bed bugs are more common causes and seasonal variation is less notable. Other, rarer causes of papular urticaria include *Cheyletiella* and rat and bird mites.

Treatment

Caregivers are often resistant to this diagnosis and therapy requires establishing their trust and agreement with the treatment plan. Accompanied by behavior modifications to decrease scratching, oral antihistamines and application of high-potency topical steroid under occlusion leads to improvement in most cases. All efforts at treatment should be accompanied by the use of insect repellants to prevent exposure to new bites. Definitive management of bed bug infestation will require extermination by a professional who is familiar with the treatment of these insects¹¹³ and all pets should be appropriately treated for fleas.

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Figures 2, 3, 8, 10, 12 and 23 are available online at [Expert Consult.com](https://www.expertconsult.com) 

KEY REFERENCES

2. Steinbach WJ, Roilides E, Berman D, et al. Results from a prospective, international, epidemiologic study of invasive candidiasis in children and neonates. *Pediatr Infect Dis J* 2012;31:1252–7.
31. Greenberg RG, Benjamin DK, Gantz MG. Empiric antifungal therapy and outcomes in extremely low birth weight infants with invasive candidiasis. *J Pediatr* 2012;161:264–9.
59. Bernier V, Weill FX, Hirigoyen V, et al. Skin colonization by *Malassezia* species in neonates: a prospective study and relationship with neonatal cephalic pustulosis. *Arch Dermatol* 2002;138:215–18.
74. Woodruff CA, Hebert AA. Neonatal primary cutaneous aspergillosis: case report and review of the literature. *Pediatr Dermatol* 2002;19: 439–44.
80. Ambrosioni J, Bouchuiguir-Wafa K, Garbino J. Emerging invasive zygomycosis in a tertiary care center: epidemiology and associated risk

- factors. *Int J Infect Dis* 2010;14(Suppl. 3): e100–3.
93. Gilaberte Y, Rezusta A, Gil J, et al. Tinea capitis in infants in their first year of life. *Br J Dermatol* 2004;151:886–90.
101. Geary RJ, Lucky AW. Tinea pedis in children presenting as unilateral inflammatory lesions of the sole. *Pediatr Dermatol* 1999;16(4):255–8.
108. Peterson CM, Eichenfield LF. Scabies. *Pediatr Ann* 1996;25:97–100.
113. Shmidt E, Levitt J. Dermatologic infestations. *J Int J Dermatol* 2012;51:131–41.
149. Vetter RS, Visscher PK. Bites and stings of medically important venomous arthropods. *Int J Dermatol* 1998;37:481–96.

REFERENCES

- Ruiz-Diez B, Martinez V, Alvarez M, et al. Molecular tracking of *Candida albicans* in a neonatal intensive care unit: long-term colonization versus catheter-related infections. *J Clin Microbiol* 1997;35:3032–6.
- Steinbach WJ, Roilides E, Berman D, et al. Results from a prospective, international, epidemiologic study of invasive candidiasis in children and neonates. *Pediatr Infect Dis J* 2012;31:1252–7.
- Shattuck KE, Cochran CK, Zabransky RJ, et al. Colonization and infection associated with *Malassezia* and *Candida* species in a neonatal unit. *J Hosp Infect* 1996;34:123–9.
- Benjamin DK Jr, Stoll BJ, Fanaroff AA, et al; on behalf of the National Institute of Child Health and Human Development Neonatal Research Network. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics* 2006;117:84–92.
- Marodi L. Local and systemic host defense mechanisms against *Candida*: immunopathology of candidal infections. *Pediatr Infect Dis J* 1997;16:795–801.
- Marodi L, Kaposzta R, Campbell DE, et al. Candidacidal mechanisms in the human neonate. Impaired IFN-gamma activation of macrophages in newborn infants. *J Immunol* 1994;153:5643–9.
- Baley JE. Neonatal candidiasis: the current challenge. *Clin Perinatol* 1991;18:263–80.
- Baley JE, Kliegman RM, Fanaroff AA. Disseminated fungal infections in very low-birth-weight infants: clinical manifestations and epidemiology. *Pediatrics* 1984;73:144–52.
- Stuart SM, Lane AT. *Candida* and *Malassezia* as nursery pathogens. *Semin Dermatol* 1992;11:19–23.
- Shetty SS, Harrison LH, Hajjeh RA, et al. Determining risk factors for candidemia among newborn infants from population-based surveillance: Baltimore, MD, 1998–2000. *Pediatr Infect Dis J* 2005;24:601–4.
- Benjamin DK Jr, DeLong ER, Steinbach WJ, et al. Empirical therapy for neonatal candidemia in very low birthweight infants. *Pediatrics* 2003;112:543–7.
- Saiman L, Ludington E, Pfaller M, et al. Risk factors for candidemia in neonatal intensive care unit patients. National Epidemiology of Mycosis Survey Study Group. *Pediatr Infect Dis J* 2000;19:319–24.
- Feja KN, Wu F, Roberts K, et al. Risk factors for candidemia in critically ill infants: a matched case-control study. *J Pediatr* 2005;147:156–61.
- Kurgansky D, Sweren R. Onychomycosis in a 10-week-old infant. *Arch Dermatol* 1990;126:1371.
- Darmstadt GL, Dinulos JG, Miller Z. Congenital cutaneous candidiasis: clinical presentation, pathogenesis, and management guidelines. *Pediatrics* 2000;105:438–44.
- Raval DS, Barton LL, Hansen RC, Kling PJ. Congenital cutaneous candidiasis: case report and review. *Pediatr Dermatol* 1995;12:355–8.
- Clegg HW, Prose NS, Greenberg DN. Nail dystrophy in congenital cutaneous candidiasis. *Pediatr Dermatol* 2003;20:342–4.
- Gerberding KM, Eisenhut CC, Engle WA, et al. Congenital *Candida* pneumonia and sepsis: a case report and review of the literature. *J Perinatol* 1989;9:159–61.
- Johnson DE, Thompson TR, Ferrieri P. Congenital candidiasis. *Am J Dis Child* 1981;135:273–5.
- Waguespack-LaBiche J, Chen SH, Yen A. Disseminated congenital candidiasis in a premature infant. *Arch Dermatol* 1999;135:510–12.
- Cosgrove BF, Reeves K, Mullins D, et al. Congenital cutaneous candidiasis associated with respiratory distress and elevation of liver function tests: a case report and review of the literature. *J Am Acad Dermatol* 1997;37:817–23.
- Santos LA, Beceiro J, Hernandez R, et al. Congenital cutaneous candidiasis: Report of four cases and review of the literature. *Eur J Pediatr* 1991;150:336–8.
- Baley JE, Silverman RA. Systemic candidiasis: cutaneous manifestations in low birthweight infants. *Pediatrics* 1988;82:211–15.
- Pradeepkumar VK, Rajadurai VS, Tan KW. Congenital candidiasis: varied presentations. *J Perinatol* 1998;18:311–16.
- Rowen JL, Atkins JT, Levy ML, et al. Invasive fungal dermatitis in the < or = 1000-gram neonate. *Pediatrics* 1995;95:682–7.
- Hay RJ, Baran R. Fungal (onychomycosis) and other infections of the nail apparatus. In: Dawber RP, editor. *Diseases of the nails and their management*. Oxford: Blackwell Scientific; 1984. p. 121–56.
- Reddy TC, Chakrabarti A, Singh M, et al. Role of buffy coat examination in the diagnosis of neonatal candidemia. *Pediatr Infect Dis J* 1996;15:718–20.
- Flynn PM, Cunningham CK, Kerker T, et al. Oropharyngeal candidiasis in immunocompromised children: a randomized, multicenter study of orally administered fluconazole suspension versus nystatin. Multicenter Fluconazole Study Group. *J Pediatr* 1995;127:322–8.
- Crutchfield CE III, Lewis EJ. The successful treatment of oral candidiasis (thrush) in a pediatric patient using itraconazole. *Pediatr Dermatol* 1997;14:246.
- Stevens DA. Oral amphotericin B as an antifungal agent. *J Mycol Med* 1997;7:241–2.
- Greenberg RG, Benjamin DK, Gantz MG. Empiric antifungal therapy and outcomes in extremely low birth weight infants with invasive candidiasis. *J Pediatr* 2012;161:264–9.
- Rowen JL, Tate JM. Management of neonatal candidiasis. Neonatal Candidiasis Study Group. *Pediatr Infect Dis J* 1998;17:1007–11.
- Leibovitz E. Neonatal candidosis: clinical picture, management controversies and consensus, and new therapeutic options. *J Antimicrob Chemother* 2002;49:69–73.
- van den Anker JN, van Popele NM, Sauer PJ. Antifungal agents in neonatal systemic candidiasis. *Antimicrob Agents Chemother* 1995;39:1391–7.
- Friedlich PS, Steinberg I, Fujitani A, et al. Renal tolerance with the use of intralipid-amphotericin B in low-birth-weight neonates. *Am J Perinatol* 1997;14:377–83.
- Scarcella A, Pasquariello MB, Giugliano B, et al. Liposomal amphotericin B treatment for neonatal fungal infections. *Pediatr Infect Dis J* 1998;17:146–8.
- Linder N, Klinger G, Shalit I, et al. Treatment of candidemia in premature infants: comparison of three amphotericin B preparations. *J Antimicrob Chemother* 2003;52:663–7.
- Juster-Reicher A, Flidel-Rimon O, Amitay M, et al. High-dose liposomal amphotericin B in the therapy of systemic candidiasis in neonates. *Eur J Clin Microbiol Infect Dis* 2003;22:603–7.
- Fasano C, O'Keeffe J, Gibbs D. Fluconazole treatment of neonates and infants with severe fungal infections not treatable with conventional agents. *Eur J Clin Microbiol Infect Dis* 1994;13:351–4.
- Schwarze R, Penk A, Pittrow L. [Use of fluconazole in children less than 1 year old: review]. *Mycoses* 1998;41:61–70.
- Melville C, Kempley ST. Treatment of invasive *Candida* infection in neonates with congenital cutaneous candidiasis. *Pediatrics* 2001;108:216.
- Aleck KA, Bartley DL. Multiple malformation syndrome following fluconazole use in pregnancy: report of an additional patient. *Am J Med Genet* 1997;72:253–6.
- Warren NG, Hazen KC. *Candida*, *Cryptococcus*, and other yeasts of medical importance. *Manual of clinical microbiology*. Washington, DC: ASM Press; 2006. p. 723–37.
- de Repentigny L, Ratelle J, Leclerc JM, et al. Repeated-dose pharmacokinetics of an oral solution of itraconazole in infants and children. *Antimicrob Agents Chemother* 1998;42:404–8.
- Tosti A, Piraccini BM, Vincenzi C, et al. Itraconazole in the treatment of two young brothers with chronic mucocutaneous candidiasis. *Pediatr Dermatol* 1997;14:146–8.
- Sciaccia A, Betta P, Cilauro S, et al. [Oral administration of itraconazole in a case of neonatal hepatic candidiasis]. *Pediatr Med Chir* 1995;17:173–5.
- Stein DH. Fungal, protozoan, and helminth infections. In: Schachner LA, Hansen RG, editors. *Pediatric dermatology*. New York: Churchill Livingstone; 1995. p. 1295–345.
- Odio CM, Araya R, Pinto LE, et al. Caspofungin therapy of neonates with invasive candidiasis. *Pediatr Infect Dis J* 2004;23:1093–7.
- McCoy M, Bedwell S, Noori S. Exchange of peripherally inserted central catheters is associated with an increased risk for bloodstream infection. *Am J Perinatol* 2011;28:419–24.
- Colby CE, Drohan L, Benitz W, et al. Low yield of ancillary diagnostic studies in neonates infected with *Candida*. *J Perinatol* 2004;24:241–6.
- Neely MN, Schreiber JR. Fluconazole prophylaxis in the very low birthweight infant: not ready for prime time. *Pediatrics* 2001;107:404–5.
- Long SS, Stevenson DK. Reducing *Candida* infections during neonatal intensive care: management choices, infection control, and fluconazole prophylaxis. *J Pediatr* 2005;147:135–41.
- Kicklighter SD, Springer SC, Cox T, et al. Fluconazole for prophylaxis against candidal rectal colonization in the very low birthweight infant. *Pediatrics* 2001;107:293–8.
- Bertini G, Perugi S, Dani C, et al. Fluconazole prophylaxis prevents invasive fungal infection in high-risk, very low birthweight infants. *J Pediatr* 2005;147:162–5.
- Healy CM, Baker CJ, Zaccaria E, et al. Impact of fluconazole prophylaxis on incidence and

- outcome of invasive candidiasis in a neonatal intensive care unit. *J Pediatr* 2005;147:166–71.
56. Blyth CC, Barzi F, Hale K. Chemoprophylaxis of neonatal fungal infections in very low birth-weight infants: efficacy and safety of fluconazole and nystatin. *J Paediatr Child Health* 2012;48:846–51.
 57. Leeming JP, Sutton TM, Fleming PJ. Neonatal skin as a reservoir of *Malassezia* species. *Pediatr Infect Dis J* 1995;14:719–21.
 58. Ashbee HR, Leck AK, Puntis JW, et al. Skin colonization by *Malassezia* in neonates and infants. *Infect Control Hosp Epidemiol* 2002;23:212–16.
 59. Bernier V, Weill FX, Hirigoyen V, et al. Skin colonization by *Malassezia* species in neonates: a prospective study and relationship with neonatal cephalic pustulosis. *Arch Dermatol* 2002;138:215–18.
 60. Bergman JN, Eichenfield LF. Neonatal acne and cephalic pustulosis: is *Malassezia* the whole story? *Arch Dermatol* 2002;138:255–7.
 61. Welbel SF, McNeil MM, Pramanik A, et al. Nosocomial *Malassezia pachydermatis* bloodstream infections in a neonatal intensive care unit. *Pediatr Infect Dis J* 1994;13:104–8.
 62. Chang HJ, Miller HL, Watkins N, et al. An epidemic of *Malassezia pachydermatis* in an intensive care nursery associated with colonization of health care workers' pet dogs. *N Engl J Med* 1998;338:706–11.
 63. Terragni L, Lasagni A, Oriani A, et al. Pityriasis versicolor in the pediatric age. *Pediatr Dermatol* 1991;8:9–12.
 64. Di Silverio A, Zeccara C, Serra F, et al. Pityriasis versicolor in a newborn. *Mycoses* 1995;38:227–8.
 65. Rapalano R, Mortureux P, Couprie B, et al. Neonatal *Malassezia furfur* pustulosis. *Arch Dermatol* 1996;132:190–3.
 66. Dankner WM, Spector SA, Fierer J, et al. *Malassezia fungemia* in neonates and adults: complication of hyperalimentation. *Rev Infect Dis* 1987;9:743–53.
 67. Marcon MJ, Powell DA. Human infections due to *Malassezia* spp. *Clin Microbiol Rev* 1992;5:101–19.
 68. Salazar GE, Campbell JR. Trichosporonosis, an unusual fungal infection in neonates. *Pediatr Infect Dis J* 2002;21:161–5.
 69. Gokahmetoglu S, Nedret KA, Gunes T, et al. Case reports. *Trichosporon mucoides* infection in three premature newborns. *Mycoses* 2002;45:123–5.
 70. Antachopoulos C, Papakonstantinou E, Dotis J. Fungemia due to *Trichosporon asahii* in a neutropenic child refractory to amphotericin B. *J Pediatr Hematol Oncol* 2005;27:283–5.
 71. Walsh TJ, Melcher GP, Rinaldi MG, et al. *Trichosporon beigelii*, an emerging pathogen resistant to amphotericin B. *J Clin Microbiol* 1990;28:1616–22.
 72. Perparim K, Nagai H, Hashimoto A, et al. In vitro susceptibility of *Trichosporon beigelii* to antifungal agents. *J Chemother* 1996;8:445–8.
 73. Maples HD, Stowe CD, Saccente SL, et al. Voriconazole serum concentrations in an infant treated for *Trichosporon beigelii* infection. *Pediatr Infect Dis J* 2003;22:1022–4.
 74. Woodruff CA, Hebert AA. Neonatal primary cutaneous aspergillosis: case report and review of the literature. *Pediatr Dermatol* 2002;19:439–44.
 75. Groll AH, Jaeger G, Allendorf A, et al. Invasive pulmonary aspergillosis in a critically ill neonate: case report and review of invasive aspergillosis during the first 3 months of life. *Clin Infect Dis* 1998;27:437–52.
 76. Steinbach WJ. Pediatric aspergillosis: disease and treatment differences in children. *Pediatr Infect Dis J* 2005;24:358–64.
 77. Denning DW. Invasive aspergillosis. *Clin Infect Dis* 1998;26:781–803.
 78. Robertson AF, Joshi VV, Ellison DA, et al. Zygomycosis in neonates. *Pediatr Infect Dis J* 1997;16:812–15.
 79. Linder N, Keller N, Huri C, et al. Primary cutaneous mucormycosis in a premature infant: case report and review of the literature. *Am J Perinatol* 1998;15:35–8.
 80. Ambrosioni J, Bouchuiguir-Wafa K, Garbino J. Emerging invasive zygomycosis in a tertiary care center: epidemiology and associated risk factors. *Int J Infect Dis* 2010;14(Suppl. 3):e100–3.
 81. Holzel H, Macqueen S, MacDonald A, et al. *Rhizopus microsporus* in wooden tongue depressors: a major threat or minor inconvenience? *J Hosp Infect* 1998;38:113–18.
 82. du Plessis PJ, Wentzel LF, Delport SD, et al. Zygomycotic necrotizing cellulitis in a premature infant. *Dermatology* 1997;195:179–81.
 83. Hughes C, Driver SJ, Alexander KA. Successful treatment of abdominal wall *Rhizopus* necrotizing cellulitis in a preterm infant. *Pediatr Infect Dis J* 1995;14:336.
 84. Amin SB, Ryan RM, Metlay LA, et al. *Absidia corymbifera* infections in neonates. *Clin Infect Dis* 1998;26:990–2.
 85. Roilides E, Zaoutis TE, Walsh TJ. Invasive zygomycosis in neonates and children. *Clin Microbiol Infect* 2009;15(Suppl. 5):50–4.
 86. Weitzman I, Chin NX, Kunjuku N, et al. A survey of dermatophytes isolated from human patients in the United States from 1993 to 1995. *J Am Acad Dermatol* 1998;39:255–61.
 87. Weston WL, Morelli JG. Neonatal tinea capitis. *Pediatr Infect Dis J* 1998;17:257–8.
 88. Snider R, Landers S, Levy ML. The ringworm riddle: an outbreak of *Microsporum canis* in the nursery. *Pediatr Infect Dis J* 1993;12:145–8.
 89. Johnson ML, Anderson LL. Papulosquamous plaques in a mother and newborn son. *Pediatr Dermatol* 1995;12:281–4.
 90. Romano C, Gianni C, Papini M. Tinea capitis in infants less than 1 year of age. *Pediatr Dermatol* 2001;18:465–8.
 91. Virgili A, Corazza M, Zampino MR. Atypical features of tinea in newborns. *Pediatr Dermatol* 1993;10:92.
 92. Cabon N, Moulinier C, Taieb A, et al. Tinea capitis and faciei caused by *Microsporon lanuginosum* in two neonates. *Pediatr Dermatol* 1994;11:281.
 93. Gilaberte Y, Rezusta A, Gil J, et al. Tinea capitis in infants in their first year of life. *Br J Dermatol* 2004;151:886–90.
 94. Singal A, Baruah MC, Rawat S, et al. *Trichophyton rubrum* infection in a 3-day-old neonate. *Pediatr Dermatol* 1996;13:488–9.
 95. Ghorpade A, Ramanan C, Durairaj P. *Trichophyton mentagrophytes* infection in a two-day-old infant. *Int J Dermatol* 1991;30:209–10.
 96. Baudraz-Rosselet F, Ruffieux P, Mancarella A, et al. Diaper dermatitis due to *Trichophyton verrucosum*. *Pediatr Dermatol* 1993;10:368–9.
 97. Ploysangam T, Lucky AW. Childhood white superficial onychomycosis caused by *Trichophyton rubrum*: report of seven cases and review of the literature. *J Am Acad Dermatol* 1997;36:29–32.
 98. Proudfoot L, Higgins EM, Morris-Jones R. A retrospective study of the management of pediatric kerion in *Trichophyton tonsurans* infection. *Pediatr Dermatol* 2011;28:655–7.
 99. Alden ER, Chernila SA. Ringworm in an infant. *Pediatrics* 1969;44:261–2.
 100. Jang KA, Chi DH, Choi JH, et al. Tinea pedis in Korean children. *Int J Dermatol* 2000;39(1):25–7.
 101. Geary RJ, Lucky AW. Tinea pedis in children presenting as unilateral inflammatory lesions of the sole. *Pediatr Dermatol* 1999;16(4):255–8.
 102. Mercurio MG, Silverman RA, Elewski BE. Tinea capitis: fluconazole in *Trichophyton tonsurans* infection. *Pediatr Dermatol* 1998;15:229–32.
 103. Elewski BE, Caceres HW, DeLeon L, et al. Terbinafine hydrochloride oral granules versus oral griseofulvin suspension in children with tinea capitis: results of two randomized, investigator-blinded, multicenter, international, controlled trials. *J Am Acad Dermatol* 2008;59(1):41–54.
 104. Lipozencic J, Skerlev M, Orofino-Costa R, et al. A Randomized, double-blind, parallel group, duration-finding study of oral terbinafine and open-label, high-dose griseofulvin in children with tinea capitis due to *Microsporum* species. *Br J Dermatol* 2002;146(5):816–23.
 105. Pierard GE, Arrese JE, Pierard-Franchimont C. Treatment and prophylaxis of tinea infections. *Drugs* 1996;52:209–24.
 106. Rabinowitz LG, Esterly NB. Naftifine (Naftin) in pediatrics. *Pediatrics* 1992;90:652.
 107. Friedlander SF, Suarez S. Pediatric antifungal therapy. *Dermatol Clin* 1998;16:527–37.
 108. Peterson CM, Eichenfield LF. Scabies. *Pediatr Ann* 1996;25:97–100.
 109. Haim A, Grunwald MH, Kapelushnik J, et al. Hyper eosinophilia in red scaly infants with scabies. *J Pediatr* 2005;146:712.
 110. Camassa F, Fania M, Ditano G, et al. Neonatal scabies. *Cutis* 1995;56:210–12.
 111. Duran C, Tamayo L, de la Luz OM, et al. Scabies of the scalp mimicking seborrheic dermatitis in immunocompromised patients. *Pediatr Dermatol* 1993;10:136–8.
 112. Huffam SE, Currie BJ. Ivermectin for *Sarcoptes scabiei* hyperinfestation. *Int J Infect Dis* 1998;2:152–4.
 113. Schmidt E, Levitt J. Dermatologic infestations. *J Int J Dermatol* 2012;51:131–41.
 114. Ko CJ, Elston DM. Pediculosis. *J Am Acad Dermatol* 2004;50:1–12.
 115. Elston DM. Drugs used in the treatment of pediculosis. *J Drugs Dermatol* 2005;4:207–11.
 116. Idriss S, Levitt J. Malathion for head lice and scabies: treatment and safety considerations. *J Drugs Dermatol* 2009;8:715–20.
 117. Nolan K, Kamrath J, Levitt J. Lindane toxicity: a comprehensive review of the medical literature. *Pediatr Dermatol* 2012;29:141–6.
 118. Downs AM, Stafford KA, Harvey I, et al. Evidence for double resistance to permethrin and malathion in head lice. *Br J Dermatol* 1999;141:508–11.
 119. Stough D, Shellabarger S, Quiring J, et al. Efficacy and safety of spinosad and permethrin creme rinses for pediculosis capitis (head lice). *Pediatrics* 2009;124:e389–95.
 120. McCormack PL. Spinosad: in pediculosis capitis. *Am J Clin Dermatol* 2011;12:349–53.

121. Goates BM, Atkin JS, Wilding KG, et al. An effective nonchemical treatment for head lice: a lot of hot air. *Pediatrics* 2006;118:1962–70.
122. Pearlman DL. A simple treatment for head lice: dry-on, suffocation-based pediculicide. *Pediatrics* 2004;114:e275–9.
123. Barker SC, Altman PM. An ex vivo, assessor blind, randomised, parallel group, comparative efficacy trial of the ovicidal activity of three pediculicides after a single application – melaleuca oil and lavender oil, eucalyptus oil and lemon tea tree oil, and a ‘suffocation’ pediculicide. *BMC Dermatol* 2011;11:14.
124. Chosidow O, Giraudeau B, Cottrell J, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med* 2010;362:896–905.
125. Roberts RJ, Casey D, Morgan DA, et al. Comparison of wet combing with malathion for treatment of head lice in the UK: a pragmatic randomised controlled trial. *Lancet* 2000;356:540–4.
126. Mumcuoglu KY, Klaus S, Kafka D, et al. Clinical observations related to head lice infestation. *J Am Acad Dermatol* 1991;25:248–51.
127. Izri A, Chosidow O. Efficacy of machine laundering to eradicate head lice: recommendations to decontaminate washable clothes, linens, and fomites. *Clin Infect Dis* 2006;42:E9.
128. Castanet J, Monpoux F, Mariani R, et al. Demodicidosis in an immunodeficient child. *Pediatr Dermatol* 1998;14:219–20.
129. Patrizi A, Neri I, Chiericato C, et al. Demodicidosis in immunocompetent young children: report of eight cases. *Dermatology* 1997;195:239–42.
130. Sarro RA, Hong JJ, Elgart ML. An unusual demodicidosis manifestation in a patient with AIDS. *J Am Acad Dermatol* 1998;38:120–1.
131. Noutsis C, Millikan LE. Myiasis. *Dermatol Clin* 1994;12:729–36.
132. Bapat SS. Neonatal myiasis. *Pediatrics* 2000;106:E6.
133. Koh TH. Neonatal myiasis: a case report and a role of the Internet. *J Perinatol* 1999;19:528–9.
134. Boyer KM. Diagnosis and treatment of congenital toxoplasmosis. *Adv Pediatr Infect Dis* 1996;11:449–67.
135. Lynfield R, Guerina NG. Toxoplasmosis. *Pediatr Rev* 1997;18:75–83.
136. Justus J. Cutaneous manifestations of toxoplasmosis. *Curr Probl Dermatol* 1971;4:24–47.
137. Safadi MA, Berezin EN, Farhat CK, et al. Clinical presentation and follow up of children with congenital toxoplasmosis in Brazil. *Brazil J Infect Dis* 2003;7:325–31.
138. Carvalheiro CG, Mussi-Pinhata MM, Yamamoto AY, et al. Incidence of congenital toxoplasmosis estimated by neonatal screening: relevance of diagnostic confirmation in asymptomatic newborn infants. *Epidemiol Infect* 2005;133:485–91.
139. Roizen N, Swisher CN, Stein MA, et al. Neurologic and developmental outcome in treated congenital toxoplasmosis. *Pediatrics* 1995;95:11–20.
140. Alger LS. Toxoplasmosis and parvovirus B19. *Infect Dis Clin North Am* 1997;11:55–75.
141. Kubba R, Al Gindan Y. Leishmaniasis. *Dermatol Clin* 1989;7:331–51.
142. Di rocco M, Vignola S, Borroni C, et al. Cutaneous leishmaniasis in a 6-month-old girl. *J Pediatr* 1998;132:748.
143. del Giudice P, Marty P, Lacour JP, et al. Cutaneous leishmaniasis due to *Leishmania infantum*. Case reports and literature review. *Arch Dermatol* 1998;134:193–8.
144. Reed BR, Orton PW, Marr JJ, et al. Cutaneous leishmaniasis in an infant. *Pediatr Dermatol* 1983;1:142–5.
145. Wittner M. Leishmaniasis. In: Feigin RD, Cherry JD, editors. *Textbook of pediatric infectious diseases*. Philadelphia: WB Saunders; 1998. p. 2452–8.
146. Nelson JD, editor. 1998–1999 Pocket book of pediatric antimicrobial therapy. 13th ed. Baltimore: Williams & Wilkins; 1998. p. 62.
147. Brimhall CL, Esterly NB. Summertime, and the critters are biting. *Contemp Pediatr* 1994;11:62–77.
148. Rees RS, King LE Jr. Arthropod bites and stings. In: Fitzpatrick TB, editor. *Dermatology in general medicine*. New York: McGraw-Hill; 1987. p. 2495–506.
149. Vetter RS, Visscher PK. Bites and stings of medically important venomous arthropods. *Int J Dermatol* 1998;37:481–96.
150. Doggett SL, Geary MJ, Russell RC. The resurgence of bed bugs in Australia: with notes on their ecology and control. *Environ Health* 2004;4:30–8.
151. Delaunay P, Blanc V, Del Giudice P, et al. Bedbugs and infectious diseases. *Clin Infect Dis* 2011;52:200–10.

Eczematous Disorders

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Introduction

Eczematous eruptions represent a significant proportion of the skin diseases affecting neonates and infants. Clinically they are characterized by erythema, edema, scale, and sometimes crusts. The most common disorder is atopic dermatitis (AD) and, in fact, the term ‘eczema’ (which means ‘boiling over’) is often used by laymen to refer to AD. Seborrheic dermatitis and irritant dermatitis also frequently affect infants, while allergic contact dermatitis (ACD) is less common. Some nutritional, metabolic, and immunologic diseases have clinical manifestations that include eczematous eruptions which may be difficult to differentiate from AD, and they require a high index of suspicion for their occurrence.

Atopic dermatitis

Atopic dermatitis is a chronic, pruritic skin condition with a frequently relapsing course. It was first described by Besnier in 1892 as ‘prurigo diasthétique’. In 1933, Wise and Sulzberger coined the term ‘atopic dermatitis’, and Hill and Sulzberger characterized the clinical entity 2 years later.^{1,2} AD is notable for inflammation, xerosis, crusts, excoriations, and lichenification, and it is the most common chronic inflammatory dermatosis of early childhood. The disease imposes an enormous burden on the personal, social, emotional, and financial resources of patients and their families. In the USA, annual direct costs for AD care are estimated at US\$1–4 billion,³ which does not include the effects of lost productivity such as missed work and school days nor the impact on quality of life.

The prevalence of AD has increased markedly over the past 50 years, with current rates of 15–29% in the USA, Europe, Japan, and other industrialized countries and lower but increasing rates in developing nations.^{4–6} AD affects individuals of all races, with several studies showing a slightly higher prevalence in black children.⁶ However, different countries with similar ethnic demographics have markedly different recorded prevalences, supporting the concept that environmental factors are important in disease expression.⁷ AD may be slightly more common in girls (female: male ratio of 1.3:1), although some studies note that it affects the sexes approximately equally.⁸

RISK FACTORS

Multiple epidemiologic studies have examined risk factors for disease development. Only two factors show consistent, strong association: a family history of atopic diseases (i.e., asthma, allergic rhinitis, atopic dermatitis) and loss of function mutations in the *filaggrin* (*FLG*) gene. A positive family history of atopy is noted in approximately 70% of affected individuals.

The odds of developing AD are 2–3-fold higher in children with one atopic parent, and this increases to as high as 3–5-fold if both parents are atopic.^{9,10} Some have noted a maternal history of AD itself to be more predictive.^{11,12} The *FLG* gene encodes a key protein involved in terminal differentiation of the epidermis, and its breakdown products are important in the formation of the skin barrier, including the stratum corneum, and natural moisturizing factor (see below). Loss of function mutations confer a risk for earlier-onset AD, as well as for more severe disease.¹³

AD is more frequent in higher social and socioeconomic classes.¹⁴ Other factors that may be associated with a greater risk for disease include small family size, migration from rural to urban environments, and increased parental education.⁷ Some have noted a higher incidence in association with maternal smoking and elevated birthweight, though not all studies corroborate these findings.^{15,16} The effect of exposure to pets in the home is unclear, due to conflicting data.^{17,18}

CLINICAL FINDINGS

History

The onset of disease is most commonly between 3 and 6 months of age, with approximately 60% of patients developing the eruption within the first year of life and 90% by 5 years of age.^{19,20} Atopic dermatitis is usually the first manifestation of the ‘atopic march,’ which refers to the subsequent development of food allergies, asthma, and allergic rhinitis, although this progression does not happen in all individuals and/or the sequence may vary.²⁰ More recently, eosinophilic esophagitis and gastroenteritis have been added to the list of associated disorders.²¹

The predominant symptom is pruritus, which is difficult to control and a major cause of morbidity and poor quality of life for both the child and caregiver.²² It frequently interferes with sleep and can lead to complications such as secondary infection of excoriated lesions. Parents should be questioned about the infant scratching and rubbing against objects such as bedding or carpeting. Unfortunately, these actions further incite inflammation and the itch sensation, leading to a vicious cycle.²³

Physical examination

There are three age-related phases to AD: infantile, childhood, and adult disease. During each phase both the sites of involvement and the morphology of the lesions change, although the phases often overlap. The infantile phase generally lasts until 2–3 years of age, the childhood phase from 2 years until puberty, and the adult phase from puberty onward.

In infancy, AD characteristically begins on the cheeks (Figs 15.1, 15.2) and scalp (Fig. 15.3) and evolves over time to involve the lateral and extensor aspects of the arms and legs (Fig. 15.4).



Figure 15.1 Atopic dermatitis with typical early facial involvement.



Figure 15.2 Acute inflammatory lesions on the face.

The periauricular areas are often affected and can lead to infra-auricular fissuring.²⁴ While the trunk may have lesions, the diaper area is usually spared due to the retention of moisture and protection from rubbing and external triggers provided by these coverings (Figs 15.5, 15.6). Lesions are symmetric, scaly, erythematous patches and plaques, within which crusting is common. Acute lesions are more exudative. Lymphadenopathy may be noted and reflects local inflammation. During late infancy and the childhood phase, the flexural surfaces of the extremities become the most commonly involved sites, particularly the antecubital and popliteal fossae (Fig. 15.7). Other frequently involved locations include the neck, wrist and ankle flexures, and the creases between the thighs and buttocks. Lesions continue to be erythematous patches and plaques with crusting, but often there is increased excoriation. Chronic findings, such as lichenification (enhanced skin markings) and pigmentary changes start to become prominent (Fig. 15.8). The pigmentary alterations (hypo- or hyperpigmentation) often evoke parental concerns about scarring, although lesions

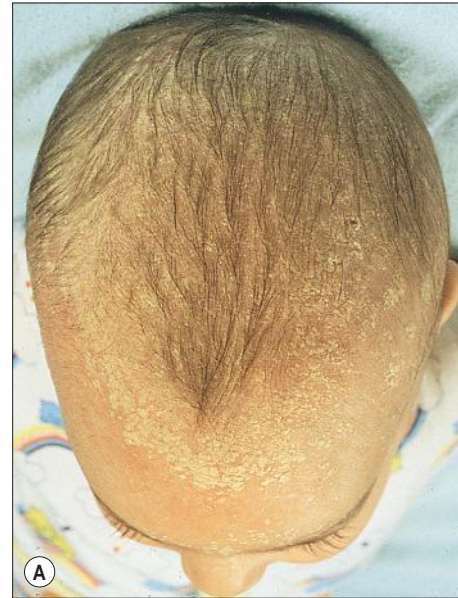


Figure 15.3 (A) Scalp scaling (akin to 'cradle cap') may be the first manifestation of atopic dermatitis. (B) Temporary alopecia may result from rubbing the sides of the head against the bedding to alleviate itching.

generally do not leave scars unless severely infected or deeply excoriated. From puberty onwards, AD lesions tend to prefer the face, back, wrists, hands, and dorsal feet.

There are a number of additional physical findings that, if present, aid in the diagnosis of atopic dermatitis (Box 15.1). These include other conditions associated with xerotic skin, such as ichthyosis vulgaris, keratosis pilaris, and pityriasis alba. Follicular lichenification with papules may be noted, especially in those with darker skin type. These are not specific to AD, however, and may be seen in otherwise healthy individuals as well. Other findings suggestive of an atopic diathesis that become more prominent with rubbing or scratching include an additional line or groove in the lower eyelid (the Dennie-Morgan fold), infraorbital darkening ('allergic shiners'), and a prominent horizontal nasal crease ('allergic salute').



Figure 15.4 (A) Extensor involvement with lichenification and crusting of the leg. (B) Erythema, scale, and crust on the extensor surface of the arm.

DIAGNOSIS

The diagnosis of AD is made clinically. This is often more challenging in early infancy, when it can be difficult to distinguish AD from other infantile eczematous disorders. Family history is often helpful and absence of an atopic disorder in the family history makes the diagnosis much less likely, though does not preclude its occurrence. The most recognized diagnostic criteria are those proposed by Hanifin and Rajka in 1980, but the four major and 23 minor criteria are too numerous to be used routinely in clinical practice.²⁵ Several expert groups have



Figure 15.5 Truncal atopic dermatitis with erythema, papules, and mild scaling.



Figure 15.6 Atopic dermatitis tends to spare the diaper area due to the retention of moisture and protection provided by the coverings.



Figure 15.7 Atopic dermatitis extending to the flexural surface of the antecubital fossa.



Figure 15.8 Marked postinflammatory hypopigmentation from AD lesions, which is common in darkly pigmented infants.

BOX 15.1 FEATURES OF ATOPIC DERMATITIS

MAJOR FEATURES

- Pruritus
- Rash on face and/or extensors in infants and young children
- Lichenification in flexural areas in older children
- Tendency toward chronic or chronically relapsing dermatitis
- Personal or family history of atopic disease: asthma, allergic rhinitis, atopic dermatitis

OTHER COMMON FINDINGS

- Dryness
- Dennie–Morgan folds (accentuated lines or grooves below the margin of the lower eyelid)
- Allergic shiners (darkening beneath the eyes)
- Facial pallor
- Pityriasis alba
- Keratosis pilaris
- Ichthyosis vulgaris
- Hyperlinearity of palms and soles
- White dermatographism (white line appears on skin within 1 min of being stroked with blunt instrument)
- Conjunctivitis
- Keratoconus
- Anterior subcapsular cataracts
- Elevated serum IgE
- Immediate skin test reactivity

Reproduced from Bernard LA, Eichenfield LF. How to identify atopic dermatitis vs. other eczemas. In: Leung DYM, Eichenfield LF, eds. Pediatric eczemas. New York: Summit Communications; 2004:20.

proposed more condensed sets of criteria,^{26–28} including the following,²⁷ which is applicable to both children and adults:

- A. Essential features (must be present)
 - a. Pruritus
 - b. Eczematous dermatitis (acute, subacute or chronic)
 - i. Typical morphology and age-specific patterns
 - ii. Chronic or relapsing history

- B. Important features (seen in most cases, adding support to the diagnosis)
 - a. Early age of onset
 - b. Atopy
 - i. Personal and/or family history
 - ii. IgE reactivity
 - c. Xerosis
- C. Associated features (these clinical associations help to suggest the diagnosis of AD but are too nonspecific to be used to define or detect AD for research or epidemiologic studies)
 - a. Atypical vascular responses (e.g., facial pallor, white dermatographism, delayed blanch response)
 - b. Keratosis pilaris/hyperlinear palms/ichthyosis
 - c. Ocular/periorbital changes
 - d. Other regional findings (e.g., perioral changes/periauricular lesions)
 - e. Perifollicular accentuation/lichenification/prurigo lesions.

To date, there is no specific laboratory test to confirm the diagnosis of AD. Serum immunoglobulin E (IgE) is elevated in approximately 70–80% of patients, although even severe cases may have normal levels.²³ The majority of patients also have increased circulating eosinophils. Recent discoveries of novel T-lymphocyte subsets and cytokine proteins have generated additional candidate markers. Thymus and activation-regulated chemokine (TARC, also called CCL17) is one such molecule suggested to increase with disease activity.²⁹ However, to date, none have demonstrated adequate sensitivity and specificity to serve as a biomarker for the disease or its response to therapy. Laboratory testing is thus seldom needed in the routine evaluation of uncomplicated AD.

Skin biopsies may be helpful in distinguishing AD from other inflammatory skin disorders, but the biopsy findings are not pathognomonic. The histology varies from an acute dermatitis with spongiosis and a perivascular lymphocytic infiltrate, to chronic changes in lichenified skin showing acanthosis, hyperkeratosis, and accumulation of Langerhans' cells, macrophages, and mast cells in addition to lymphocytes around blood vessels. The superficial venular plexus has endothelial cell hypertrophy, basement membrane thickening, and increased numbers of immunoreactive nerve fibers.^{30,31} Eosinophils are not commonly present in acute AD, but are increased in number in chronic lesions. Mast cells may be normal to increased, and in different stages of degranulation.

ETIOLOGY AND PATHOGENESIS

The pathogenesis of AD involves a complex interplay of genetic, immunologic, infectious, and other environmental factors. While still not completely understood, it appears to entail two major defective processes: dysfunction of the epidermal barrier and dysregulation of the immune system. Which process occurs first to initiate disease ('outside-in' vs 'inside-out') is an ongoing debate, although it is clear that they interact and exacerbate one another. This is compounded by a heightened response to environmental allergens, irritants, and microbial antigens.^{31,32}

For many years, it has been known that AD involves genetic susceptibility, given familial clustering, concordance in monozygotic twins but discordance in dizygotic twins, and reports of transfer of AD by bone marrow transplantation.^{33,34} It has been most highly linked to genes of the epidermal differentiation

complex located on chromosome 1q21, particularly the *FLG* gene, which is also the main cause of ichthyosis vulgaris. The association of *FLG* mutations with AD is one of the most robust known for complex genetic disorders.¹³ Large, population-based studies have identified over 35 mutations in affected individuals, with distinct mutations in different ethnic groups.³⁵ As mentioned above, loss of function mutations are associated with early-onset and more severe, persistent disease, and additionally appear to give increased allergic sensitization and total IgE levels, a greater risk for asthma and food and other allergies, and a higher incidence of skin infections with herpes simplex virus (eczema herpeticum). But despite the strong association, *FLG* null mutations are seen in only approximately 18–48% of individuals with AD (depending on the population) and conversely, about 40% of individuals with such mutations do not develop the disease.¹³ Genetic screening of affected families has highlighted other chromosome regions that contribute to disease susceptibility, including cytokine and immune-related genes (e.g., those encoding interleukins (IL)-4, -5, and -13 and the regulated on activation of normal T-cell expressed and secreted (RANTES) chemotactic cytokine), genes encoding innate immunity receptors (e.g., the genes for toll-like receptors (TLR)-2 and -9), and genes implicated in other inflammatory diseases (e.g., those encoding nucleotide-binding oligomerization domain protein (NOD)-1 and NOD2).^{36,37} There are likely additional genes that remain to be discovered, and of those already identified to have high disease association, a number still require determination of exact function.

Defects in both the structure and function of the epidermal barrier are present in AD. *FLG* mutations lead to disorganized keratin filaments and abnormal architecture of the lamellar bilayer and assembly of the cornified envelope. Decreased filaggrin breakdown products affect levels of natural moisturizing factor and the skin pH, resulting in increased transepidermal water loss and skin permeability. In addition, barrier function is markedly reduced due to a decline in ceramide levels, which are major water-retaining molecules, and from an imbalance of proteolytic enzymes that affect epidermal adhesion and their anti-protease counterparts.^{35,38} Abnormalities in tight junction expression that form a second barrier in the stratum granulosum further add to the pathology.³⁴ These factors all lead to dry, xerotic skin, while facilitating entry of antigens through the damaged epidermis that stimulate cutaneous inflammation.

Immunologic abnormalities are another major pathogenic mechanism. Antigens bind to and activate epidermal Langerhans' cells and dermal dendritic cells. Circulating T cells that have increased expression of the cutaneous lymphocyte-associated antigen (CLA) receptor home to the skin, where they are primed by these antigen-presenting cells. In the acute phase of disease, these activated T cells overexpress cytokines of the Th2 class, notably IL-4 and IL-13, which mediate switching of immunoglobulin isotypes to IgE synthesis and upregulated expression of adhesion molecules on endothelial cells. IL-4 also stimulates mast cells to produce mediators such as histamine. IL-5 predominates in subsequent stages and is involved in eosinophil development and survival.^{31,39} While AD begins acutely as a Th2-mediated disorder, in its chronic phase it is characterized by Th0 cells (cells that share some activities of both Th1 and Th2 cells) and Th1 cells; associated cytokines include interferon- γ . The switch to Th0/1 cells involves the infiltration of the epidermis by inflammatory dendritic epidermal cells (IDEC) and production of IL-12 and IL-18, as well as

several remodeling-associated cytokines. Also of significance is an increase in Th22 cells in chronic AD skin, which produce IL-22 that inhibits terminal differentiation and induces epidermal hyperplasia.⁴⁰ Additional T cell subsets have been identified, but their roles in AD remain to be fully defined. T regulatory cells with normal immunosuppressive activity appear to be expanded in the peripheral blood of patients, but not in lesional skin or atopy patch test sites. Th17 cells have been found to be elevated in patients with acute AD, but not as prominently as in psoriasis.³¹

Enhanced allergen penetration through the damaged epidermis gives increased production of thymic stromal lymphopoietin (TSLP) by keratinocytes, which may be a critical link between the barrier and immune defects. TSLP has been shown to drive both the initial Th2 cytokine response and the switch to the Th0/1 phenotype.³⁹ Mechanical injury such as scratching or rubbing, microbes, and proinflammatory cytokines themselves further stimulate release of TSLP, thus perpetuating the inflammation. The immunologic response contributes to additional barrier abnormalities, since IL-4 and IL-13 are known to suppress filaggrin expression and downregulate proper processing of profilaggrin.

Antigens that gain entry include microbes. The antimicrobial barrier is compromised in AD from a combination of the defective physical barrier, an increased pH which may allow greater adherence and multiplication of bacteria, and toll-like receptor defects which diminish recognition of microbial agents. In addition, the increase in Th2 cytokines suppresses the synthesis of antimicrobial peptides by keratinocytes, specifically LL-37 (cathelicidin) and β -defensins 2 and 3.⁴¹ This predisposes atopic individuals to widespread skin infections due to bacteria and viruses (including herpes, molluscum, and vaccinia), and possibly to dermatophytes. *Staphylococcus aureus*, in particular, can trigger multiple inflammatory cascades. Staphylococcal toxins activate T cells in a superantigen-driven fashion and induce IgE-specific responses. These further skew the immune response toward Th2 cytokine production and explain the association of *S. aureus* infection with exacerbations of AD.⁴² The superantigens also cause a profound reduction in steroid responsiveness of T cells, giving another possible mechanism for disease flares. Exogenous protease inhibitors produced by *S. aureus* may also damage the epidermal barrier, thereby potentiating the absorption of allergens into the skin and leading to increased bacterial colonization.

The impact of food exposure on the development of atopic dermatitis is controversial. Although it is known that food allergy and sensitization more commonly develop in children with atopic dermatitis, it is unclear how important food exposures are to the onset and course of atopic dermatitis, nor how common food-induced eczematous dermatitis is during infancy.⁴³ Aeroallergens may also trigger immune responses, but sensitization is usually after infancy. The house-dust mite, *Dermatophagoides pteronyssinus*, has been cited in the pathogenesis of AD, but measures to decrease dust mite exposure are not necessarily protective.⁴⁴ *Malassezia* yeasts have also been suggested but not confirmed to cause exacerbations of disease.

The mechanisms underlying pruritus in AD are the subject of much investigation. In addition to histamine, several other mediators, such as neuropeptides, kinins, and cytokines, can induce pruritus. Studies have shown that the number of sensory and neuropeptide-containing nerve fibers is increased in lesional AD skin.^{30,45} Mast cells store large amounts of proteases,

including tryptase, which may induce pruritoceptive itch when released in the proximity of these nerve fibers. These release stress-induced neuropeptides in parallel, which might activate mast cells through neurokinin receptors to perpetuate pruritic signals. The Th2 response contributes via increased levels of IL-31, which has recently been found to enhance pruritus. Staphylococcal superantigens also markedly enhance IL-31 production.^{45,46}

DIFFERENTIAL DIAGNOSIS

The common disorders in the differential diagnosis of AD include seborrheic dermatitis, contact dermatitis, psoriasis, scabies, ichthyosis, tinea corporis, and keratosis pilaris (Box 15.2). In early infancy, seborrheic dermatitis may be virtually indistinguishable from AD due to the similarity in sites of involvement and morphology (Fig. 15.9). Irritant dermatitis is not uncommon, but allergic contact dermatitis is rare in the newborn period, although it may affect infants. A configuration suggesting an external source of exposure may be evident and helpful in determining the presence of a contact dermatitis.

Psoriasis is not as common in infancy, but psoriasis vulgaris and pustular psoriasis may occur (see Chapter 16). In the case of psoriasis vulgaris, the diaper area is most commonly affected and consists of erythematous, well-demarcated plaques

surmounted by some to little scale, which is less thick and silvery relative to other sites due to moisture and occlusion. About 5% of children appear to an overlap of psoriasis and atopic dermatitis lesions, and often have a family history of both disorders.⁴⁷

Scabies may sometimes be difficult to distinguish from AD because both can cause severe pruritus, but it is rarely considered in the newborn, and is more relevant to infants. Here the face is not usually involved, whereas eczematous patches on the cheeks and xerosis are typical of AD. Moreover, the eruption of scabies has polymorphous lesions, including burrows, papules, nodules, eczematous and urticarial lesions, as well as pustules on the palms and soles. A recent onset of itching in family members is also helpful in differentiating the two conditions.

When the skin lesions are associated with failure to thrive, diarrhea, infection, and/or signs in other organ systems, it is important to consider systemic disorders, such as nutritional and metabolic abnormalities, and genetic conditions including immunodeficiency (Box 15.3). Also in the differential diagnosis are proliferative disorders, most notably Langerhans' cell histiocytosis, which often includes hemorrhagic lesions. Occasionally, AD may be so severe that the whole body becomes erythrodermic, causing confusion with other causes of erythroderma, particularly Netherton syndrome and nutritional deficiencies (see Chapter 18).

PROGNOSIS

Data from follow-up surveys show enormous variation in the long-term course and prognosis of AD, owing to differences in patient sampling techniques. Vickers⁴⁸ reported that AD cleared by age 20 in 90% of patients, but the inclusion of infants with seborrheic dermatitis, which resolves within weeks to months, biased these results. Wüthrich⁴⁹ found that of 121 infants followed to a mean of 23.5 years, 11% had resolution in childhood,

BOX 15.2 DIFFERENTIAL DIAGNOSIS OF INFANTILE ATOPIC DERMATITIS: COMMON DISORDERS

- Seborrheic dermatitis
- Contact dermatitis (allergic and irritant)
- Scabies
- Psoriasis
- Ichthyosis vulgaris
- Keratosis pilaris



Figure 15.9 It can be difficult to distinguish seborrheic dermatitis from atopic dermatitis in young infants, but over time the diagnosis becomes evident given greater persistence and pruritus with AD (which this child developed).

BOX 15.3 DIFFERENTIAL DIAGNOSIS OF INFANTILE ATOPIC DERMATITIS: RARE DISORDERS

NUTRITIONAL AND METABOLIC DISORDERS

- Acrodermatitis enteropathica
- Zinc deficiency (prematurity; deficient breast milk zinc; cystic fibrosis)
- Other nutritional deficiencies (biotin, essential fatty acids)
- Hartnup disease
- Phenylketonuria
- Prolidase deficiency
- Gluten-sensitive enteropathy
- Hurler syndrome

PRIMARY IMMUNODEFICIENCY DISORDERS

- Hyperimmunoglobulin-E syndrome
- Severe combined immunodeficiency disorder/Omenn syndrome
- Wiskott–Aldrich syndrome
- Agammaglobulinemia

OTHER INHERITED DISORDERS WITH IMMUNE DEFECTS

- Netherton syndrome
- Ataxia–telangiectasia

ADDITIONAL CONDITIONS

- Langerhans' cell histiocytosis

an additional 25% cleared in adolescence, but 32% had a chronic continuous course from infancy into adulthood and 20% had reappearance of disease in adolescence. Despite these differences, there is a steady decline in AD prevalence over the childhood years. Up to 60–70% resolution of disease by adulthood appears to be a reasonable estimate, with an overall prevalence rate of 2–10% in adults.^{49,50}

Early onset within the first 6 months of life, greater disease severity, and persistence into adolescence are predictors that the disease is more likely to continue into adult life.⁵¹ Other reported risk factors for adult disease include the presence of other atopic conditions such as asthma and allergic rhinitis, a family history of AD in parents or siblings, high serum IgE levels, and *FLG* null mutations in early-onset cases.^{49,51} It is, however, difficult to precisely predict if and when a particular child will have resolution or remission and management should continue until there is notable quiescence of lesions. But even after what appears to be resolution, easily irritated or dry skin may persist or hand eczema may affect the individual later in life.⁵²

Figures on the incidence of asthma and allergic rhinitis following or in association with AD vary from 10–70%.^{51,53} In one survey, 36% suffered from allergic rhinitis, 28% from asthma, and 15% from both.⁵⁴ There is an increased risk of developing asthma or AD if there is a family history of either condition. Higher rates have also been reported with more severe AD, with 60% having asthma and 62% with allergic rhinitis reported in one study.⁵⁵ Mechanisms to link their occurrence are under study. Filaggrin mutations appear to increase the risk of development of asthma and other atopic conditions.^{13,53} It has been suggested that early or severe AD and epicutaneous sensitization to environmental allergens may lead to inflammation and development of allergic disease on re-exposure at other epithelial barrier sites (e.g., the respiratory or gastrointestinal tract). Systemic circulation of keratinocyte-derived TSLP may play an important role in this process.⁵⁶ Although supported by animal models, this remains to be confirmed, along with whether prevention or early treatment of AD mitigates subsequent development of other atopic conditions.

TREATMENT

The management of AD should be directed at reducing signs and symptoms of disease and decreasing the frequency and severity of flares. It requires a multimodal approach that includes meticulous general skin care, hydration of the skin, avoidance of potential irritants and allergens, and reduction of pruritus and inflammation. Secondary infections should be treated and prevented. It is extremely important to educate the parents on the chronic nature of the disease, as many seek an immediate cure which is not possible. The goals of therapy, including the benefits, risks, and side effects of treatments, should be detailed. Because parents are inundated with much information, careful attention to detail, repetition of advice, and written handouts and action plans can improve treatment outcomes. Educational programs in the form of structured, multidisciplinary classes and nursing-led care are themselves effective primary interventions that can give some decrease in disease severity.⁵⁷

Xerosis/dry skin

Xerosis is a significant component of the disease, and hydrating the skin is a foundation of atopic dermatitis therapy. This is

accomplished through frequent application of emollients or moisturizers and care in bathing techniques. The appropriate frequency of bathing is controversial, but limiting to a short duration using warm rather than hot water is recommended. Bathing alone leads to a decrease in hydration status of the skin once the water evaporates.⁵⁸ On the other hand, there is evidence that bathing followed by the immediate application of an emollient while the skin is wet (the ‘soak and seal’ method) has an excellent hydrating effect, while removing scale and crust, and can be a tremendously useful treatment measure for patients during flares.^{59,60}

The application of emollients and moisturizers independent of bathing can also improve hydration status, enhance barrier function, and be steroid sparing.^{59,61} They should be applied all over the body and after topical corticosteroids have been applied to lesional skin. There is no one preferred emollient or moisturizing agent. Ideally, it should be safe, effective, inexpensive, and free of additives, fragrances, and other potential sensitizing agents. Ointments are the thickest agents but creams and oils may also be used, while lotions should generally be avoided as they are less effective in decreasing xerosis. Products containing urea, lactic acid, and α -hydroxy acids may sting and their absorption in infants is unknown.

Topical therapies have been developed to target skin barrier dysfunction and replace abnormal epidermal lipids. These include preparations having distinct compositions of lipids and ceramides to mimic endogenous lipids, and creams containing palmitoylethanolamide, hydro lipids, and/or filaggrin breakdown products.⁶² While they have shown some benefit and may be helpful as adjuvant agents, the few studies performed to date have not demonstrated superiority relative to traditional, less expensive options such as petrolatum ointment.^{62,63} But addressing the defective barrier is an important therapeutic concept, given the current understanding of AD pathogenesis.

Anti-inflammatory agents

Topical corticosteroids. Topical corticosteroids were first introduced by Sulzberger and Witten in 1952 and remain a mainstay of AD treatment because of their excellent anti-inflammatory effects. They are grouped according to potency into seven classes, from very weak (VII) to superpotent (I). There is often fear and reluctance on the part of parents to use them, despite the extremely small number of reported side-effects in those treated, the majority of which have occurred in patients receiving inappropriate treatment.^{64,65} Physicians should encourage the correct use of topical corticosteroid preparations on affected inflamed areas. Both amount and potency are important and close monitoring during treatment is appropriate for safety and compliance. Precise information should be given to the parents regarding the manner of application, and written instructions are very useful.

There are many methods of prescribing topical corticosteroids and other anti-inflammatory therapies. Published algorithms are available and may be used.⁶⁶ Mild cases and/or facial or diaper areas are generally treated with low-potency steroids. For more significant flares, or if low-potency steroids are inadequate to control the disease, more potent topical corticosteroids are used for truncal and body surfaces. For severe flares, wet-wrap therapy (a damp layer of gauze or clothing with an outer dry layer) may be utilized with low- to mid-strength topical steroids for several days to increase their effect.⁶⁷ Prescriptions should be given for sufficient treatment of the area

involved, but with more caution and set limits with higher potency agents. In general, one finger-tip unit (the amount from the distal interphalangeal joint to the finger tip, ~0.5 g) should be applied over an area of two adult palms.^{64,68} For acute flares, areas should be treated until the inflammation disappears, with frequent and liberal use of emollients. Most should be used twice a day, although some agents are designated for once-daily use. Emollients should be continued after corticosteroids are discontinued and may help lessen disease recurrence and the need for anti-inflammatory agents.

Systemic corticosteroids, particularly long-term use, are not indicated for the treatment of AD in neonates or infants. In addition to hypothalamic-pituitary-adrenal axis suppression, they can affect linear growth and have known rebound and other negative effects.

Topical calcineurin inhibitors. Topical calcineurin inhibitors are another class of anti-inflammatory therapy for atopic dermatitis. In the USA, topical tacrolimus and pimecrolimus are approved as second-line agents for short-term and non-continuous chronic use in children aged 2 years and older, but they are sometimes used off-label. Unlike topical steroids, topical calcineurin inhibitors do not carry a risk of skin atrophy, and therefore may be helpful for sites of thinner skin (i.e., eyelids, face, and diaper area where steroid atrophy are a bigger concern) or to decrease the use of topical steroids in those with moderate or severe disease. There is histologic evidence that while both classes improve epidermal differentiation and decrease transepidermal water loss, topical steroids do not restore the epidermal barrier structures (e.g., lamellar body extrusion and lipid bilayer formation in the lower stratum corneum) to the same extent as calcineurin inhibitors.⁶⁹

The most common side-effects with topical calcineurin inhibitors are local reactions such as stinging and burning, although this may improve after several applications or when first preceded by a short period of topical corticosteroid use. Patients should be monitored for signs and symptoms of cutaneous viral infections, although ongoing surveillance has not shown a consistent increase in frequency.^{70,71} These agents do carry a boxed warning stating that their long-term safety has not been established because of rare post-marketing cases of malignancy, specifically, of skin cancer and lymphoma. Interim analyses of ongoing, 10-year surveillance studies to address these concerns have not found evidence of increased malignancy rates relative to that expected in the general pediatric population.^{72,73} Several studies, including a large case-control study of 293 253 patients, have found an increased risk of lymphoma that correlates with AD severity, but not with topical calcineurin inhibitor use.^{74,75}

Maintenance therapy. After obtaining clearance/control of a flare, the goal is to prolong the period until the next flare with a long-term maintenance regimen, as well as to establish a rescue strategy in the event of disease relapse. The maintenance regimen may use emollients, newer barrier cream therapies, intermittent topical corticosteroids, and/or topical calcineurin inhibitors, depending on disease severity and frequency. For sites with frequent recurrence, proactive therapy can be beneficial, where a topical anti-inflammatory agent is used on a scheduled intermittent basis 2–3 times weekly on clear or almost clear skin, rather than waiting until the disease recurs. Randomized controlled trials using topical steroids and topical calcineurin

inhibitors in this manner have noted a reduction in relapse risk, fewer exacerbations, and increased time to first recurrence, without significant adverse effects.⁷⁶

Pruritus

One of the major challenges of treatment is controlling the intense pruritus, which also causes sleep deprivation in both patients and their family members. Though commonly prescribed, there is little supportive evidence for effectiveness of antihistamines in decreasing actual itch or disease.⁷⁷ Sedating H₁ antihistamines likely help by causing drowsiness from central nervous system (CNS) depression. Nonsedating antihistamines show variable results in controlling AD-associated pruritus and are more helpful for urticaria, dermatographism, and rhinitis. Effective decrease of skin inflammation and increased measures for hydration are the most effective interventions at this time to reduce pruritus.⁴⁵ But with ongoing study of the mechanisms underlying pruritus, additional targets for therapy are being identified (e.g., IL-31 and the H₄ histamine receptor on Th2 cells that mediates its release, prostaglandins, and neuropeptides such as substance P).

Environmental control

Dry skin, excessive sweating, changes in temperature and humidity, and exogenous irritants and allergens are all triggers of eczema that are influenced by the environment.⁷⁸ Skin hyper-reactivity in infants with atopic dermatitis is common, allowing factors that are not often discernible to induce pruritus and the 'itch-scratch' cycle that may cause eczema flares. Avoidance of known triggers and irritants is an important part of therapy, although based more on expert opinion than robust supportive evidence. Neonates with AD are irritated by coarse fibers, such as wool; 100% cotton clothing is traditionally recommended, although similar smooth-fibered clothing, such as commercially available silk fabrics, may also be used.⁷⁹ As reviewed, bathing followed by emollients can minimize skin dryness, and also lessen vulnerability to irritants, allergens and microbes. Mattress covers, low-pile carpet in sleeping areas, and non-dander-producing pets may be beneficial for patients in whom aeroallergens are suspected of playing a causative role, particularly for children with concomitant asthma and/or rhinitis.^{78,80} But it should be emphasized that such measures may not result in clearance of AD, though avoidance of known triggers is a reasonable approach in management.

Infections

Staphylococcus aureus frequently colonizes the skin and nares of atopic individuals. Topical corticosteroids alone can reduce bacterial counts.⁸¹ Oral antibiotics may be necessary to treat obvious secondary bacterial infection due to *S. aureus* and/or *Streptococcus pyogenes*, presenting as pustules or honey-colored crusts. The use of antibiotics for AD flares without clear infection is more controversial.⁸² Although prolonged oral antibiotic therapy is alleged to reduce the *S. aureus* superantigens, resistant bacteria may develop. The usual first-line systemic treatment is a first- or second-generation cephalosporin. Macrolides are of limited utility, with significant antibiotic resistance reported in most geographic areas. Methicillin-resistant *S. aureus* (MRSA) is a growing concern, although there are data for both increased and decreased rates of MRSA in atopic patients relative to the general population.^{83,84} If MRSA infection is suspected, oral clindamycin or trimethoprim-sulfamethoxazole are reasonable

options. Bacterial culture and sensitivities may be needed to guide antibiotic therapy.

Mupirocin (pseudomonic acid) decreases the carrier rate of *S. aureus* on the skin, but application in large areas is impractical. Irritation and potential toxicity limit the use of antibacterial scrubs in neonates and young infants. Dilute bleach baths (0.005% is recommended and equals 3 cc/gallon of water) have been used to reduce the staphylococcal colony count, and one study showed decreased disease severity when used with intranasal mupirocin in children with frequent secondary infections.⁸⁵ Recolonization does occur, but there may be less concern with resistance with use of dilute bleach relative to other topical and systemic antibiotics that may be needed long term for other indications.⁷⁵ Topical hypochlorite products are also available as an alternative to dilute bleach baths, but at higher cost.

Atopic individuals are also more prone to secondary infection with the herpes simplex virus (eczema herpeticum) and this should be suspected when there are vesiculopustular lesions or 'punched-out' erosions. Children with *FLG* mutations, more severe AD disease, and/or with other atopic conditions are at greatest risk.⁸⁶ Systemic antivirals are needed, with hospitalization and intravenous treatment warranted with systemic symptoms or widespread lesions.

It may also be more difficult to rid extensive common or flat warts or molluscum contagiosum in atopic individuals. Vaccination against smallpox is contraindicated in persons with AD, even when the dermatitis is in remission. In infants and young children, the greater concern is secondary contraction by contact with a recently vaccinated individual. Widespread and even fatal vaccinia can occur in patients with an atopic diathesis and counseling is important for family members who may be considered for vaccination (now selectively reinstituted due to threats of bioterrorism), particularly military personnel. A new smallpox vaccine using a replication-incompetent modified vaccinia virus is being studied, with preliminary safety and efficacy in patients with AD.⁸⁷

Addressing diet and potential allergens

As discussed, food-induced eczematous dermatitis is controversial, and the more common scenario is that of food allergy occurring concomitantly with AD. Food exposures in allergic children tend to induce type I hypersensitivity reactions such as urticaria, contact urticaria, and non-cutaneous allergy symptoms such as gastrointestinal effects, wheezing, and nasal congestion. Egg, milk, wheat, soy, and peanuts account for more than 90% of the foods producing allergies in children with AD.⁸⁰ It is important to note that while food allergies are usually associated with positive immediate skin tests or elevated serum IgE specific to various foods, positive tests do not necessarily correlate with a clinically important allergy.

In 2010, a National Institute of Allergy and Infectious Diseases (NIAID) expert panel published guidelines stating that a reproducible adverse health effect (i.e., skin, gastrointestinal, or respiratory symptoms) must occur with exposure to constitute a food allergy.⁸⁸ Testing for the five foods above is recommended for children less than 5 years of age with moderate to severe AD *only* if they have either: persistent disease despite appropriate therapy or a reliable history of an immediate reaction after ingestion of a specific food. In the absence of documented or proven food allergy, it is not recommended to avoid potentially allergenic foods as a means of managing AD. Extensive elimination diets are rarely, if ever, necessary because even in patients

with multiple positive skin tests or moderate to severe disease, the majority do not show a reaction on controlled challenge.^{78,89}

Cases of malnutrition and kwashiorkor have been reported due to unnecessary, pre-emptive dietary avoidance.⁹⁰ Thus, if food allergies are suspected, testing and dietary modification should be performed carefully under the supervision of an allergy specialist. Positive in vitro tests should be confirmed with controlled food challenges and re-testing performed with older age, as children will often develop tolerance to milk, egg, soy, and wheat, over time.

Adjunctive and alternative therapies

Families of patients with atopic dermatitis often use alternative therapies. In one study, the second most common reason for patients to seek alternative medicine was for treatment of allergic conditions such as atopic dermatitis.⁹¹ In many cases, the safety and efficacy of these treatments have not been established, although the number of published reports evaluating such therapies is increasing. Larger, long-term randomized trials are needed in order to determine safety, efficacy, optimal dosing, and treatment duration before such therapies can be recommended, particularly in infants. Chinese herbal therapy is the modality most extensively studied for the treatment of AD. A number of controlled trials have been conducted, but results have been mixed and inconclusive.^{92,93} There are also significant safety concerns: a number of cases of serious hepatotoxicity have been reported with their use for AD and some topical forms of these herbal medications have been found to be contaminated with corticosteroids.

Essential fatty acid supplementation has also been studied for use in AD. It is theorized that the disturbed barrier function in the skin of these patients may be caused by altered metabolism of fatty acids and that this disturbance could potentially be treated with agents high in certain fatty acids. These include, among others, evening primrose oil, fish oil, and borage oil. Results to date have been mixed, and there is not sufficient evidence to support their use.⁹³ Other alternative therapies include acupuncture, massage therapy, hypnotherapy, transepidermal nerve stimulation, biofeedback, and other oral herbal supplements, but supportive data for their use in infantile AD are scant.

PRIMARY PREVENTION

Despite attempts to mitigate risk, there are no known methods that effectively prevent the development of AD. Prebiotic and probiotic use in pregnant mothers and infants has given conflicting results, with dosing, timing, and the type of probiotic given varying greatly among studies.⁹⁴ Prolonged or exclusive breast-feeding beyond the recommended first 4–6 months of infancy does not convincingly impact the development of disease and there is even some suggestion of a higher risk of AD with longer duration of breast-feeding. Maternal avoidance diets during pregnancy and the lactation period and delayed introduction of solid foods (including possible allergenic foods) also have not decreased the incidence of disease. There has been a modest but inconsistent benefit with the use of hydrolyzed protein formulas compared with cow's milk formulas.^{95,96}

More recently, research has turned to skin barrier protection in the newborn period to prevent AD. One open-label, prospective pilot study of at least daily use of a common over-the-counter emollient and petrolatum in high-risk newborns found

that 3 of 20 (15%) developed disease during the follow-up period.⁹⁷ While similar high-risk cohorts have a reported 30–50% rate of AD by age 2, the time of follow-up of this study was not adequate for comparison and the small sample size was an additional limiting factor. Nevertheless, early barrier protection for the primary prevention of AD is an intriguing concept under further investigation.

Seborrheic dermatitis

First described by Unna in 1887, seborrheic dermatitis is a distinct inflammatory eruption primarily involving the head and intertriginous areas. One survey of 1116 children reported a prevalence of approximately 10% in early childhood, with the majority having minimal to mild disease.⁹⁸ Seborrheic dermatitis affects both sexes and is most common within the first 4–6 weeks of life, but may occur up to 1 year of age, followed by a rapid decline in frequency.

CUTANEOUS FINDINGS

The scalp is the first area to be involved, with greasy, yellow scale on the vertex (often called ‘cradle-cap’; Fig. 15.10) and variable erythema. Hair loss is uncommon. Lesions often affect the face, primarily the central and lower forehead, eyebrows, malar eminences, nasolabial folds, external ears, and retroauricular creases (Fig. 15.11). Other commonly affected sites include the diaper area, the axillary area and other creases (Fig. 15.12), and the presternal and interscapular areas. Well-demarcated, erythematous plaques with a variable degree of scale are noted at the diaper area and folds, whereas eczematous patches are common on the trunk.

Candida albicans can enter the affected areas, causing maceration, crusting, and at times, papules or pustules (see Chapter 14). Secondary bacterial infection may rarely occur, with crusting and pustules on the existing lesions. Post-inflammatory hypopigmentation is common in dark-skinned infants, but improves after the dermatitis has resolved.



Figure 15.10 Seborrheic dermatitis with erythema and greasy, white scale on the scalp.

ETIOLOGY AND PATHOGENESIS

Despite how common it is, the etiology and pathogenesis of seborrheic dermatitis remain unknown. Given the ages of occurrence, theories of increased sebaceous gland activity as a result of maternal hormones and nutritional factors have been proposed, but not validated.⁹⁹

Studies have implicated the yeast-like organism *Malassezia* (previously *Pityrosporum ovale*) in the etiology of seborrheic dermatitis, as the organism was detected in the majority of affected infants, but in only a few of the controls.¹⁰⁰ In treatment studies, topical ketoconazole 2% and bifonazole shampoos resulted in favorable response in most of those treated. But as *Malassezia* yeast is known to be present on all human skin, the condition may reflect an abnormal reaction in predisposed individuals.

DIAGNOSIS

The diagnosis is usually made clinically. The histology of the lesions is not diagnostic and consists of a subacute dermatitis with elongation of the epidermal rete ridges. Lymphocytes and



Figure 15.11 Seborrheic dermatitis may occasionally be more widespread.



Figure 15.12 The body folds are often involved in seborrheic dermatitis.

histiocytes are found in association with mild to moderate spongiosis and psoriasiform hyperplasia associated with parakeratosis around follicular ostia. The presence of neutrophils is more suggestive of seborrheic dermatitis than other forms of dermatitis. There are no specific laboratory markers for diagnosis of this condition.

DIFFERENTIAL DIAGNOSIS

Seborrheic dermatitis may be difficult to distinguish from psoriasis. Psoriasis in infants often starts in the diaper area with persistent, well-demarcated, erythematous plaques surmounted by scale. But the greasy scale in the scalp and creases that are typical of seborrheic dermatitis are not seen in psoriasis. Similarly, AD in newborns is easy to confuse with seborrheic dermatitis, particularly during the first few weeks of life, although the diagnosis usually becomes clear with time. The morphology of the lesions and the presence or absence of pruritus and xerosis are helpful in differentiating between the two. Seborrheic dermatitis is more likely when the axillae are affected, and AD is more likely to be the diagnosis when the shins and forearms are involved. Scalp involvement in AD has a more dry scale.

Persistent hemorrhagic, atrophic, or ulcerative lesions should alert physicians to consider the diagnosis of Langerhans' cell histiocytosis (LCH; see [Chapter 28](#)). LCH in neonates and young infants can resemble seborrheic dermatitis, given a similar distribution in the scalp and the retroauricular and diaper areas. Well-demarcated, erythematous patches and crusts are evident, but the presence of petechiae and purpura is typical of LCH. Lesions of LCH may also involve other areas of the body and with varying morphologies, including erythematous papules, vesicles, and nodules. Skin biopsy easily differentiates between the two conditions and should be performed when LCH is in the differential diagnosis, given the potential systemic implications.

Other eczematous disorders, including immunodeficiency diseases, nutritional and metabolic disorders, may appear similar to seborrheic dermatitis but will have associated infections or systemic manifestations such as diarrhea and failure to thrive.

COURSE, MANAGEMENT, TREATMENT, AND PROGNOSIS

Follow-up studies of patients with infantile seborrheic dermatitis have produced a variety of findings. Vickers⁴⁸ classified both AD and seborrheic dermatitis as one disease. Others concluded that many of the cases diagnosed as infantile seborrheic dermatitis evolved into AD. These reports may have based their diagnosis on the finding of cradle cap, which was thought to be diagnostic of seborrheic dermatitis but is now known to also frequently occur in AD.¹⁰¹ Reports of seborrheic dermatitis evolving into psoriasis may reflect the previous lack of recognition of psoriasis in infancy. Based on current understanding of the entity, infantile seborrheic dermatitis is thought to resolve over weeks to months.

Treatment of seborrheic dermatitis, when needed, consists of using a mild shampoo, such as selenium or zinc, or anti-yeast shampoos such as ketoconazole. A low-potency topical corticosteroid may be needed if more inflammatory lesions are noted. Scale can be softened before removal with an oil preparation or a weak keratolytic agent. Such measures are usually effective in

controlling the disease within several weeks. Salicylic acid preparations should not be used because absorption can cause salicylism and irritation.

Recurrence is rare in infancy. Although this is a condition known to affect adolescents and adults, there is no evidence that infantile disease predisposes to the development of the eruption later in life.

Contact dermatitis

Contact dermatitis is an inflammatory process caused by exposure either to an irritating substance or to one causing an allergic reaction of the skin. Irritant contact dermatitis occurs in many individuals who contact the offending agent, while allergic contact dermatitis occurs only in a small number of exposed individuals who become sensitized and have subsequent re-exposure. The classic picture of contact dermatitis is a scaly or vesicular pink plaque with well-defined margins corresponding to the area of contact.

IRRITANT CONTACT DERMATITIS

The severity of an irritant contact dermatitis (ICD) depends on the chemical and physical properties of the irritant, the location and condition of the skin at the time of exposure, and the concentration and duration of contact. Symptoms usually consist of burning and pain rather than itch and their onset ranges from minutes to 1–2 days post-exposure.¹⁰²

ICD of the diaper region is one of the most common eruptions of infancy. It consists of erythema with maceration and may include papules, erosions, and even ulcerations, when severe. The convex surfaces of the buttocks, genitalia, lower abdomen and upper thighs tend to be involved, while the skin folds are spared, given less exposure to sources of irritation (see [Chapter 17](#)). The constant moisture, occlusion, and friction in the diaper area make it prone to damage. This is compounded by contact with fecal proteolytic enzymes and lipases that are activated in a damp, alkaline environment, along with irritation from urine and chemicals such as soaps, detergents, and topical preparations.¹⁰³ Secondary infection with bacteria or *Candida albicans* can occur and should be addressed in management. Premature neonates, as well as infants between 9 and 12 months of age, have a higher rate of irritant diaper dermatitis.^{103,104} Underlying medical conditions or medications that cause diarrhea can increase the risk. Cases of severe erosive dermatitis with desquamation and blistering have been reported with accidental and occasional therapeutic ingestion of senna-containing laxatives by toddlers, with overnight diaper occlusion likely augmenting the reaction.¹⁰⁵

Another common site for ICD in infants is the face and particularly, the perioral area. This age group is more susceptible due to frequent drooling, the putting of hands and objects into the mouth ([Fig. 15.13](#)), and contact with wet foods during feeding.

Pathogenesis

Although inflammatory cells have a role in the development of ICD, allergen-specific immune lymphocytes are not involved in pathogenesis and prior sensitization is not necessary. Irritants all tend to lead to skin barrier disruption, epidermal cellular damage, and release of pro-inflammatory mediators.¹⁰² Keratinocytes play a major role with release of cytokines such as



Figure 15.13 Irritant contact dermatitis often affects the perioral area of infants due to frequent contact with drool, fingers, and food.

IL-1 α , IL-1 β , and tumor necrosis factor (TNF)- α , and by upregulation of major histocompatibility class II antigens and cell adhesion molecules. The chemokine CCL21 is produced by dermal lymphatic endothelial cells and facilitates the migration of naive T-lymphocytes, resulting in a cutaneous inflammatory response.¹⁰⁶

Diagnosis and differential diagnosis

The diagnosis of ICD depends on the patient history and clinical presentation. Histology is generally thought to be unhelpful, as findings vary by irritant mode of action and concentration, along with the severity and duration of the eruption. Parakeratosis and some degree of intercellular edema or spongiosis in the epidermis are often present. There may be mild dermal edema and a superficial, perivascular infiltrate of lymphocytes. Depending on the concentration of irritant, apoptotic keratinocytes may range from occasional to marked ballooning with confluent areas of necrosis. More chronic ICD has hyperkeratosis and parakeratosis, moderate to marked acanthosis, and elongation of the rete ridges. It can sometimes be difficult to clinically differentiate irritant from allergic contact dermatitis. There do not appear to be histologic findings or specific cytokines that clearly distinguish the two reactions and patch testing may be needed to exclude the latter.¹⁰²

Candidal infection of the diaper area usually gives sharply marginated, beefy-red plaques that include the skin folds. White scale may be at the border and a hallmark is the presence of satellite papules and pustules near the plaques. Psoriasis at this site gives well-demarcated, erythematous plaques that also involve the folds, but it may be difficult to diagnose except by long-term observation, especially when there is little scale. The development of more classic psoriatic lesions at other body sites or the presence of nail pitting is helpful. Diaper psoriasis also tends to be more resistant to treatment with low-potency topical anti-inflammatory agents.

Management

Efforts to avoid the causative irritant and contributory factors are key to the improvement of ICD. Gentle cleansers should be used and the area kept free from excessive moisture. Thick barrier creams or ointments can help to protect the skin from exogenous substances and accelerate barrier recovery. Petrolatum jelly is one example, and at the diaper area, zinc oxide paste

can also be helpful. Frequent diaper changes help to minimize contact with urine and stool, with superabsorbent diapers being better than cloth diapers.¹⁰⁷ Low-potency topical corticosteroids or topical calcineurin inhibitors may be needed for short courses if there is significant inflammation.

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis (ACD) was previously believed to be rare in childhood, but is now recognized to occur even in very young children, though the data in neonates and infants are limited. This may be due to increased contact sensitization as a result of exposure at younger ages to cosmetic products and piercings. One study of 321 children under 3 years of age with suspected ACD showed that 200 children (62.3%) had at least one positive reaction to 30 allergens considered as the standard pediatric series.¹⁰⁸ Nickel was the most frequent allergen, with over one-quarter of cases testing positive. The next most frequent allergens were potassium dichromate, cocamidopropyl betaine, cobalt chloride, neomycin sulfate, and methylchloroisothiazolinone/methylisothiazolinone. Rates were highest in those with truncal or widespread dermatitis.

Nickel sensitivity in neonates and infants is predominantly caused by contact with nickel snaps on clothing. The most commonly involved areas are on the center of the chest and upper abdomen, where there may be a pruritic, well-defined dermatitis corresponding to the area of contact. Id reactions may occur, particularly in the antecubital fossae. Another possible source of nickel allergy is via ear-piercing, which in some cultures is performed in very young infants.¹⁰⁸ *FLG* null mutations appear to be associated with nickel contact allergy.¹⁰⁹ Allergic contact dermatitis may also occur in the diaper area, although at much lower frequency than irritant dermatitis. It also often spares the folds. Allergens include fragrances, disperse dye, and sorbitan sesquileate, an emulsifier in topical preparations. Iodopropyl carbonate, methylchloroisothiazolinone/methylisothiazolinone, and bronopol in baby wipes, as well as mercapto compounds in the elastic borders of diapers, may also cause ACD.¹⁰⁷ ACD has been reported from contact exposure to certain car seats composed of a shiny, nylon-like material, although the exact allergen has yet to be determined.¹¹⁰

Patients with AD may be predisposed to both forms of contact dermatitis because of their impaired barrier function. However, in some studies, the rate of positive patch tests was similar in children with and without AD.¹¹¹

Sensitization may occur after only one or a few exposures to the offending agent, or it may be after years of contact. When sensitization does occur, it typically takes 10–14 days from exposure. On repeat exposure, the eruption develops within 24–48 h.¹⁰² It is pruritic, with acute lesions having more intense erythema, papulation, or vesiculation, and oozing. The lesions then become more crusted and with scale. Chronic ACD lesions tend to have lichenification and scale with little vesiculation.

Pathogenesis

ACD is produced by a T-lymphocyte-mediated, type IV, delayed hypersensitivity reaction. There are two distinct phases in its development: the induction (sensitization) phase and the elicitation phase.¹⁰² In the first phase, the allergen, usually a small molecular weight chemical (hapten or prehapten), penetrates the epidermis and binds with self-proteins to generate immunogenic complexes. The hapten and/or the complexes bind

toll-like receptors on keratinocytes and activate the innate immune response. This leads to elaboration of proinflammatory mediators, such as IL-1 β , that cause skin-resident dendritic cells to take up the hapten or haptenated proteins, further process them, and then migrate to regional lymph nodes where they present the processed peptides to naive antigen-specific T cells. These naive T cells become primed, activated, and generate a clone of differentiated effector T cells, which have skin-specific homing antigens. On repeat contact of skin-resident dendritic cells with the same hapten, the activated effector T cells are recruited back to the initial site of antigen encounter in the skin (the elicitation phase). They release proinflammatory cytokines, such as interferon- γ , and lead to the development of eczematous skin inflammation.

Diagnosis and differential diagnosis

A pruritic eruption with linearity or sharp edges, especially if on localized or exposed areas only, should raise suspicion for ACD. A careful medical and environmental exposure history are needed to try to confirm this and to elicit potential culprits. Patch testing is the gold standard to identify the external chemicals to which a person is allergic, but this is not usually performed in neonates or infants, unless the eruption is persistent or refractory to treatment. The thin-layer rapid use epicutaneous (TRUE) Test[®] is a pre-prepared, commercially available patch testing kit that tests for reactivity against 36 of the most common contact allergens. More comprehensive patch testing is indicated to identify allergies to other chemicals not found in the TRUE Test[®], or if specific allergens are of interest based on the history and clinical distribution of the dermatitis. While available patch tests are approved only for the adult population at this time, they have been used in children in studies and in the clinical setting. Patch tests are usually placed on unaffected areas on the patient's back and sometimes the arms, with removal between 24 and 48 h and evaluation at 48 h and at 72 or 96 h. However, there is some debate as to whether tests should be removed earlier or if different allergen concentrations are needed in children.¹¹² Positive tests do need correlation for clinical relevance and sometimes, further confirmed by repeat open application testing of products containing the allergen that have been in contact with the patient.

The histology of allergic contact dermatitis is similar to that of other forms of eczematous dermatitis and thus, biopsy is more helpful to rule out other non-eczematous eruptions. Early lesions have spongiosis in the epidermis that then forms vesicles. The dermis has a superficial perivascular infiltrate consisting predominately of lymphocytes and other mononuclear cells. Eosinophils are usually present, but sometimes only in small numbers. In lesions that persist, scale crust and epidermal hyperplasia develop and the dermal inflammatory cell infiltrate becomes denser. Chronic lesions may show little spongiosis but have a prominent psoriasiform hyperplasia of the epidermis.

As mentioned, ACD needs to be differentiated from ICD and atopic dermatitis, although it may also occur as a consequence of the two conditions. AD usually does not involve the diaper area.

Management

First and foremost, contact with the offending allergen should be avoided. For instance, metals containing nickel should be eliminated if allergic, including zippers and underwear with nickel snaps. Information is available online on common

products containing particular allergens (<http://truetest.com>). The American Contact Dermatitis Society also has a database that allows member physicians to create a list of products free of the allergens to which the patient is allergic. Topical corticosteroids are helpful until the inflammation has subsided, with moderate to potent agents sometimes needed. Topical calcineurin inhibitors may be useful for more sensitive sites.

Keratosis pilaris

This very common condition is seen in patients with atopic dermatitis as well as in otherwise healthy children. It is caused by perifollicular retention of scale, leading to plugging in the orifice of the hair follicle (see also Chapter 25). Affected infants and children develop small, rough, flesh-colored papules on the lateral aspects of the upper arms and thighs; the cheeks may be involved, with or without surrounding erythema (Fig. 15.14). Some have a more extensive distribution to include the trunk. Lesions are generally asymptomatic, but may become red and inflamed. Treatment is aimed at skin hydration with emollients. Mild keratolytics and exfoliants may be used, but are not curative and need careful application to avoid causing irritation. Occasionally, low potency topical steroids or topical calcineurin inhibitors may be utilized for inflamed lesions. The condition usually continues into adulthood, although some sites may improve over time.

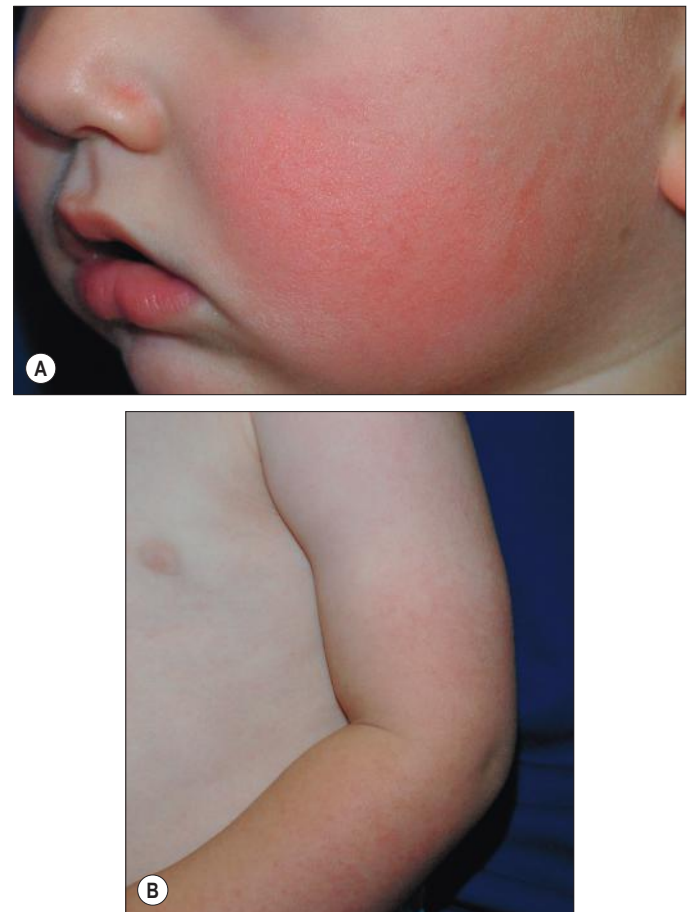


Figure 15.14 (A) Facial keratosis pilaris with small hyperkeratotic papules and surrounding erythema. (B) Keratosis pilaris is often on the extensor surfaces of the arms.

Other etiologies of eczematous eruptions (see Boxes 15.2, 15.3)

Many nutritional deficiencies, metabolic disorders, and conditions causing erythroderma may appear eczematous (see Chapter 18).

ZINC DEFICIENCY

Zinc is an essential nutrient involved in numerous biologic functions necessary for growth and development.¹¹³ Deficiency can result from inherited or acquired conditions that cause inadequate dietary intake, malabsorption, excessive loss, or a combination of these. In particular, acrodermatitis enteropathica is a rare, autosomal recessive disorder caused by an inborn error of metabolism that results in zinc malabsorption. Mutations in the *SLC39A4* gene are thought to be the underlying cause. It typically presents when the child is weaned from breast to cow's milk or in the case of formula-fed infants, after 4–10 weeks, when stores of zinc have been depleted. While both cow's and breast-milk contain adequate amounts of zinc, in acrodermatitis enteropathica the transport mechanism for intestinal absorption of zinc is defective. Absence of a binding ligand necessary for the transfer of zinc across the Paneth cells of the small intestine further contributes to deficiency.¹¹⁴

In the past, zinc deficiency resulting from inadequate intake was particularly seen in infants receiving parenteral alimentation without adequate zinc supplementation, but its routine addition to parenteral feeds has eliminated this problem. Zinc deficiency is still seen in premature infants who are exclusively breast-fed. The nutritional needs of the premature infant increase in the first few months of life, while at the same time the mother's breast-milk zinc content decreases. This may be exacerbated by increased zinc secretion into the gut and poor absorption. Zinc deficiency may also be seen in term breast-fed infants, resulting from low or completely absent zinc in the mother's breast-milk, despite normal maternal plasma zinc levels. In this instance, the transfer of zinc from plasma to breast-milk is defective. The condition may be inherited, as there are reports of absence of breast-milk zinc in multiple members of the same family.¹¹⁵

The skin eruption is usually the first clinical sign of zinc deficiency. Lesions are present on the cheeks and chin in a horseshoe distribution with erythematous, dermatitic erosions (Fig. 15.15A). Initially bullae may be present, but these rapidly erode. Over time, a more psoriasiform eruption develops. Periorbital involvement is common. A typical eruption occurs in the diaper area, consisting of a sharply demarcated area of erythema with accentuation of scale at the margin (Fig. 15.15B). The fingers and toes may have similar erosions and be accompanied by nail dystrophy. Skin lesions often become secondarily infected with *Staphylococcus aureus* and *Candida*. Overall, the eruption has a periorificial and acral pattern, though occasionally it may occur without any facial involvement. Irritability, refractory diarrhea, hair loss, and failure to thrive are additional notable clinical features.

A low plasma zinc level (<50 µg/dL) is the characteristic finding, and the level of the zinc-dependent enzyme alkaline phosphatase may also be low. Care should be taken to use a plastic syringe when drawing zinc levels and to prevent zinc contamination from rubber stoppers on glass tubes. High



Figure 15.15 Zinc deficiency dermatitis. (A) Facial eruption, including prominent periorificial involvement. (B) Diaper area. (Courtesy of Joseph Lam, MD.)

measured levels of zinc are due to laboratory error, as the body excretes zinc and limits absorption when the levels get too high.¹¹⁶

Treatment with zinc sulfate 1–3 mg/kg per day leads to rapid improvement, with irritability being the first symptom to respond.¹¹³ The inherited condition, acrodermatitis enteropathica, typically needs the higher dose of supplementation and may require long-term therapy. Occasionally, zinc sulfate causes gastrointestinal symptoms and zinc gluconate may be substituted.

BIOTIN DEFICIENCY

Biotin deficiency (multiple carboxylase deficiency) is an autosomal recessive disorder that becomes apparent in the neonatal period or late infancy. In affected neonates, the defect is a deficiency of holocarboxylase synthetase. In the later juvenile form of the disease, biotinidase is absent and leads to impairment of biotin recycling.¹¹⁷ Systemic signs and symptoms of biotin deficiency include vomiting, seizures, developmental delay, hypotonia, and eventual ataxia. Cutaneous lesions resemble those of zinc deficiency, affecting the area around the eyes, face, and perianal area. The lesions are eczematous or psoriasiform and are unresponsive to topical treatment with steroids. Secondary candidal infection is common and

remains unresponsive to treatment until the biotin deficiency is corrected.

The pathology can be attributed to the decreased activity of any or all of four critical carboxylase enzymes: 3-methylcrotonyl CoA carboxylase, propionyl CoA carboxylase, pyruvate carboxylase, and acetyl CoA carboxylase. All are biotin-dependent, where biotin acts as a cofactor. The absence of carboxylase enzymes leads to an accumulation of carboxyls in the urine, resulting in lactic acidosis or ketosis. Treatment consists of biotin 5–20 mg/day and gives rapid improvement.¹¹⁸ The biotin is well-absorbed and does not accumulate in tissues.

CYSTIC FIBROSIS

Cystic fibrosis is an autosomal recessive disorder due to defects in the *CFTR* gene, which encodes a protein that functions as a chloride channel and also regulates the flow of other ions across the apical surface of epithelial cells. The condition is characterized by widespread dysfunction of the exocrine glands, resulting in chronic pulmonary disease, pancreatic insufficiency, and elevated sweat electrolytes. It can present in neonates or young infants with an erythematous, scaly rash with periorificial and/or perineal accentuation, also closely resembling that of zinc deficiency. The exact cause of the skin eruption is unknown, although essential fatty acid deficiency, low zinc levels, and protein deficiency may all be involved.¹¹⁹ Pedal edema is common. Failure to thrive, malabsorption, hepatosplenomegaly, chronic sinus inflammation, and frequent pulmonary infections are often noted. Many newborn screens now allow early detection of cystic fibrosis. Treatment is multipronged and includes maintenance of lung function as close to normal as possible via controlling respiratory infections and clearing the airways of mucus; administration of nutritional therapy to allow adequate growth (i.e., enzyme supplements, multivitamins, and mineral supplements), and management of gastrointestinal, urogenital, and other complications. A new agent, ‘ivacaftor’, is a *CFTR* potentiator that targets the defective protein and is under study.¹²⁰

HARTNUP DISEASE

Hartnup disease is an extremely rare, heterogeneous autosomal recessive disorder characterized by a pellagra-like photosensitive eruption, cerebellar ataxia, emotional instability, encephalopathy, seizures, and aminoaciduria. The defect involves the disordered metabolism of tryptophan associated with the intestinal and renal transport of certain neutral α -amino acids. The disease is usually associated with consanguinity in the parents; it is quite rare in the Western hemisphere.¹²¹

PHENYLKETONURIA

Phenylketonuria (PKU) is a rare autosomal recessive disorder involving defective metabolism of phenylalanine (see [Chapter 23](#)). Infants may appear normal at birth, although most have blond hair and blue eyes, or are notably fairer than their parents. About 50% of patients develop a dermatitis that is indistinguishable from AD. Intellectual disability becomes evident over time, and some individuals have epilepsy or extrapyramidal manifestation.¹²² PKU is caused by the absence of phenylalanine hydroxylase, the enzyme required for conversion of phenylalanine to tyrosine. To prevent the accumulation of phenylalanine

in the blood, a low-phenylalanine diet is instituted as soon as possible after birth to prevent the resultant mental retardation. Recently, treatment with sapropterin in tetrahydrobiopterin (BH4)-responsive patients with phenylketonuria was noted to increase tolerance to dietary phenylalanine and improve quality of life.¹²³ At birth, all babies in the USA are screened for PKU.

NETHERTON SYNDROME

Netherton syndrome is a rare disorder characterized by severe generalized erythroderma, scaling, and alopecia, caused by mutations in the *SPINK-5* gene (see [Chapters 18 and 19](#), [Figs 18.4 and 19.6](#)). Sparse eyebrows and hair are a hallmark of the syndrome. Light microscopy of affected hair may reveal trichorrhexis invaginata or ‘bamboo hairs’ (see [Chapters 18 and 31](#)).

ICHTHYOSIS LINEARIS CIRCUMFLEXA

Ichthyosis linearis circumflexa is a characteristic serpiginous, migratory rash with double-edged scale that is pathognomonic and usually occurs after 2 years of age. Affected patients tend to have dramatic increases in metabolic demands due to their skin disease, often resulting in failure to thrive and/or electrolyte imbalances, including dehydration from increased insensible losses. Cutaneous and systemic infections are common. The immunologic defects include reduced memory B cells, impaired specific antibody responses, and deficient natural killer cell cytotoxicity.¹²⁴ An atopic predisposition is noted and laboratory examination often reveals elevated IgE levels. Definitive diagnosis may be made by genetic testing. Management includes emollients, careful use of keratolytics, topical steroids, and topical calcineurin inhibitors on the skin to avoid excessive systemic absorption, and antibiotics for infections.¹²⁵

OMENN SYNDROME

Omenn syndrome is an autosomal recessive form of severe combined immunodeficiency (SCID) that presents in the neonatal period with erythroderma or with an intensely pruritic, generalized eczematous eruption that can be difficult to distinguish from AD. Failure to thrive, alopecia, eosinophilia, diarrhea, and repeated infections (bacterial, viral, and fungal but particularly by *Staphylococcus aureus*) accompany the rash. Hepatosplenomegaly and lymphadenopathy are common. Bone marrow transplantation or other stem cell reconstitution is the first-line therapy for Omenn syndrome, although there are notable treatment-related complications and mortality.¹²⁶ Cyclosporine may help with the erythroderma. Interferon gamma has been administered to downregulate IL-4 and IL-5 and modulate the inflammatory reaction. Nutritional supplementation is mandatory to decrease the risk of infection and increase the likelihood of successful stem cell reconstitution. Ancillary treatment with intravenous immunoglobulin (IVIG) further decreases the risk of infection.

WISKOTT-ALDRICH SYNDROME

Wiskott–Aldrich syndrome is an X-linked recessive disease, and therefore it affects almost entirely males. A defect in the WASP protein results in defective interaction of T-lymphocytes and antigen-presenting cells such as dendritic cells and macrophages.¹²⁷ Wiskott–Aldrich syndrome presents in the first few



Figure 15.16 Wiskott-Aldrich syndrome. Eczematous dermatitis with hemorrhagic crusts.

months of life with petechiae and ecchymoses on the skin, along with a bloody diarrhea, caused by both quantitative and qualitative abnormalities of platelets. Nosebleeds are also often seen. The skin eruption, which usually develops after the bleeding diathesis, is characterized by an extremely pruritic, generalized eczematous eruption with bloody crusts (Fig. 15.16). Apart from its hemorrhagic component, the eruption is indistinguishable from AD and fulfils the Hanifin and Rajka criteria.¹²⁸ IgM deficiency is typical and there may also be cellular and humoral immunodeficiency. Skin abscesses from recurrent bacterial infections with pneumococci, meningococci, and *Haemophilus influenzae*, as well as lesions of molluscum contagiosum, verrucae, and herpes simplex, are common. Cutaneous vasculitis occurs in ~20% of patients within the first 15 years of life, and in some, presents as Henoch-Schönlein purpura with arthritis and renal involvement. There is a tendency to develop nephropathy and lymphoreticular malignancies later in life.¹²⁹ Patients with thrombocytopenia may require IVIG and/or corticosteroids, and those with bleeding may need platelet and/or red blood cell transfusions. Bone marrow transplantation can be curative in patients with a histocompatible donor.

HYPER IgE SYNDROME

Via advances in genetics, hyper-IgE syndrome is now recognized to be a group of primary immunodeficiency diseases characterized by chronic eczematous dermatitis and immune, skeletal, and dental abnormalities. The autosomal dominant form (AD-HIES) is also called Job syndrome and is due to dominant-negative mutations in the *STAT3* gene.¹³⁰ The rash has often been described as similar to AD, but in neonates



Figure 15.17 Neonates with autosomal dominant hyperimmunoglobulin-E syndrome have an inflammatory papular facial eruption.

BOX 15.4 CHARACTERISTICS OF HYPER-IgE SYNDROME

AUTOSOMAL DOMINANT HYPER-IgE SYNDROME (STAT3 MUTATION)

- Very high IgE levels, generally >2000 IU/mL, or ten times the age-appropriate normal limit
- Predominance of inflammatory facial papules in the context of an eczematous dermatitis
- Recurrent infections in childhood (staphylococcal skin, pneumonias, mucocutaneous candidiasis)
- Skeletal abnormalities (repeated fractures, osteopenia)
- Dental abnormalities (retained primary teeth)
- Characteristic 'coarse' facial features (but may not be distinctive until adolescence)
- Increased risk of malignancy, including non-Hodgkin lymphoma

AUTOSOMAL RECESSIVE HYPER-IgE SYNDROME (DOCK8 DEFICIENCY)

- Very high IgE levels, generally >2000 IU/mL, or ten times the age-appropriate normal limit
- Recurrent infections in childhood (staphylococcal skin, pneumonias), particularly recalcitrant viral skin infections
- May see skeletal and dental abnormalities but less commonly than with autosomal dominant hyper-IgE syndrome
- Increased risk of malignancy, including squamous cell carcinoma and lymphoma

inflammatory facial papules (Fig. 15.17) and pustules may predominate and initially mimic neonatal acne. The eruption often begins at or soon after birth, becomes generalized, and is usually more extensive and resistant to treatment than typical AD. The disease course usually allows differentiation between the two entities. Also characteristic of hyper-IgE syndrome are recurrent skin infections, both secondary infection of the dermatitis as well as in the form of 'cold abscesses.' These abscesses lack the warmth, redness, and tenderness of typical furuncles due to a hampered influx and impaired function of granulocytes that is a part of the syndrome. *Staphylococcus aureus* is the most common bacteria involved, but *Streptococcus*, *Haemophilus*, and enteric Gram-negative bacteria have also been isolated. AD-HIES patients may have intertriginous and retroauricular

lesions, external otitis, recurrent folliculitis especially at the upper back and shoulders, and pitted scarring of the face. Chronic mucocutaneous candidiasis affects about 60–80% of patients.^{130,131} A typical coarse facies emerges by late childhood or adolescence, with asymmetric deepened eyes, a prominent forehead and chin, and bulbous nose. The skeletal abnormalities consist of repeated fractures with minimal trauma and many also have joint hyperextensibility. Cranial synostosis and scoliosis have been reported. Dental abnormalities include retained primary teeth. As the name implies, IgE levels are quite elevated (>2000 IU/mL, or ten times the age-appropriate level), although they may decline and even normalize in adulthood. Eosinophilia (>800/mm³) is also seen. AD-HIES is complicated by recurrent episodes of pneumonia that frequently lead to pneumatoceles and bronchiectasis from aberrant healing. A higher rate of vascular anomalies, including coronary artery tortuosity and dilation, has recently been reported.¹³² There may be a higher incidence of malignancy, particularly of non-Hodgkin lymphoma.

It is now known that *DOCK8* (dedicator of cytokinesis 8) gene mutations account for nearly all of the cases categorized as autosomal recessive HIES. Features in common with AD-HIES are elevated serum IgE levels, eosinophilia, chronic dermatitis, recurrent sinopulmonary infections, and cutaneous staphylococcal abscesses. However, the dermatitis in those with *DOCK8* deficiency may not be present at birth and is often more severe, while following the classic distribution for AD (Box 15.4).^{131,133} Affected individuals also suffer from widespread, recalcitrant cutaneous viral infections (by herpes simplex, human papilloma, and molluscipox viruses) and many have asthma and food and environmental allergies. While they also have frequent pneumonia, pneumatoceles are rare. Mucocutaneous candidiasis, coarse facies, retention of primary teeth, joint hyperextensibility, and pathologic fractures are much less common in this form of hyper-IgE syndrome. There is an increased risk of malignancy, particularly of squamous cell carcinoma and lymphoma, which may be due to impaired immune surveillance and chronic viral infections in the case of squamous cell carcinoma. Reduced serum IgM levels and

lymphopenia can be noted. Mortality is often by the second to third decade of life, whereas those with AD-HIES often live into their fifth and sixth decades.¹³⁰ Thus, those with *DOCK8* deficiency need close monitoring and more frequent physical examinations.

Management of the hyper IgE syndromes involves aggressive treatment of infections and good skin care. These include topical antimicrobials and dilute bleach baths to decrease *S. aureus* colonization and systemic anti-staphylococcal antibiotic therapy to treat and prophylactically reduce skin and lung infections and abscesses. Topical steroids must be used very carefully for the dermatitis, particular in the case of *DOCK8* deficiency, where cutaneous viral infections could worsen. These viral infections are a treatment challenge, often refractory to traditional methods and with only occasional response even to systemic agents such as cidofovir and interferon alpha.¹³³ Oral antifungals are needed for those with mucocutaneous candidiasis or fungal infections of the lung, which are also difficult to eradicate. IVIG has been given to some individuals, with a few reports of reduced respiratory tract infections but not viral skin infections, and thus its use is recommended mainly for those with demonstrated impairment of antibody response. Hematopoietic stem cell transplantation has been tried for both major forms of hyper-IgE syndrome, though its exact role and timing still remain to be defined. While helpful for correction of immunodeficiency and some of the severe skin findings, there are risks with additional immunosuppression with myeloablation and prophylaxis of graft-versus-host disease, and the effects on the development of malignancy are unknown at this time.

Conclusion

Eczematous eruptions are important diagnoses to recognize, not only for their common occurrence, but also for potential systemic associations and long-term complications that require careful management in some instances.

Access the full reference list at [ExpertConsult.com](https://www.expertconsult.com) 

KEY REFERENCES

- Ricci G, Dondi A, Patrizi A. Useful tools for the management of atopic dermatitis. *Am J Clin Dermatol* 2009;10(5):287–300.
- Guttman-Yassky E, Nogales KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis – part I: clinical and pathologic concepts. *J Allergy Clin Immunol* 2011;127(5):1110–18.
- Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev* 2011;242(1):233–46.
- Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000;4(37):1–191.
- Simpson EL, Eichenfield LF, Ellis CN, et al. Current issues in atopic comorbidities and preventing the atopic march. *Semin Cutan Med Surg* 2012;31(Suppl. 3):S6–9.
- Fleischer AB Jr. Diagnosis and management of common dermatoses in children: atopic, seborrheic, and contact dermatitis. *Clin Pediatr (Phila)* 2008;47(4):332–46.
- Goskovic M, Eichenfield LF. Cutaneous findings of nutritional deficiencies in children. *Curr Opin Pediatr* 1993;5(4):441–5.
- Sillevis Smitt JH, Kuijpers TW. Cutaneous manifestations of primary immunodeficiency. *Curr Opin Pediatr* 2013;25(4):492–7.

REFERENCES

- Ricci G, Dondi A, Patrizi A. Useful tools for the management of atopic dermatitis. *Am J Clin Dermatol* 2009;10(5):287–300.
- Hill LW, Sulzberger MR. Evolution of atopic dermatitis. *Arch Derm Syphilol* 1935;32:451–63.
- Mancini AJ, Kaulback K, Chamlin SL. The socioeconomic impact of atopic dermatitis in the United States: a systematic review. *Pediatr Dermatol* 2008;25(1):1–6.
- Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368(9537):733–43.
- Odhiambo JA, Williams HC, Clayton TO, et al. ISAAC Phase Three Study Group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol* 2009;124(6):1251–1258.e23.
- Shaw TE, Currie GP, Koudelka CW, et al. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol* 2011;131(1):67–73.
- DaVeiga SP. Epidemiology of atopic dermatitis: a review. *Allergy Asthma Proc* 2012;33(3):227–34.
- Tay YK, Kong KH, Khoo L, et al. The prevalence and descriptive epidemiology of atopic dermatitis in Singapore school children. *Br J Dermatol* 2002;146:101–6.
- Wadonda-Kabondo N, Sterne JA, Golding J, et al. ALSPAC Study Team. Association of parental eczema, hayfever, and asthma with atopic dermatitis in infancy: birth cohort study. *Arch Dis Child* 2004;89(10):917–21.
- Kuster W, Petersen M, Christophers E, et al. A family study of atopic dermatitis. Clinical and genetic characteristics of 188 patients and 2,151 family members. *Arch Dermatol Res* 1990;282:98–102.
- Ruiz RG, Kemeny DM, Price JF. Higher risk of infantile atopic dermatitis from maternal atopy than from paternal atopy. *Clin Exp Allergy* 1992;22:762–6.
- Moore MM, Rifas-Shiman SL, Rich-Edwards JW, et al. Perinatal predictors of atopic dermatitis occurring in the first six months of life. *Pediatrics* 2004;113(3 Pt 1):468–74.
- McAleer MA, Irvine AD. The multifunctional role of filaggrin in allergic skin disease. *J Allergy Clin Immunol* 2013;131(2):280–91.
- Williams HC, Strachan DP, Hay RJ. Childhood eczema: disease of the advantaged? *BMJ* 1994;308:1132–5.
- Böhme M, Kull I, Bergström A, et al. Parental smoking increases the risk for eczema with sensitization in 4-year-old children. *J Allergy Clin Immunol* 2010;125(4):941–3.
- Linneberg A, Simonsen JB, Petersen J, et al. Differential effects of risk factors on infant wheeze and atopic dermatitis emphasize a different etiology. *J Allergy Clin Immunol* 2006;117(1):184–9.
- Langan SM, Flohr C, Williams HC. The role of furry pets in eczema: a systematic review. *Arch Dermatol* 2007;143:1570–7.
- Epstein TG, Bernstein DI, Levin L, et al. Opposing effects of cat and dog ownership and allergic sensitization on eczema in an atopic birth cohort. *J Pediatr* 2011;158:265–71.e1–e5.
- Queille-Roussel C, Raynaud F, Saurat J-H. A prospective computerized study of 500 cases of atopic dermatitis in childhood. *Acta Dermatol Venereol* 1985;114:87–92.
- Kuster W, Peterson M, Christophers E, et al. A family study of atopic dermatitis: Clinical and genetic characteristics of 188 patients and 2,151 family members. *Arch Dermatol Res* 1990;282:98–102.
- Jyonouchi S, Brown-Whitehorn TA, Spergel JM. Association of eosinophilic gastrointestinal disorders with other atopic disorders. *Immunol Allergy Clin North Am* 2009;29(1):85–97.
- Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. *Int J Clin Pract* 2006;60(8):984–92.
- Kabashima K. New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritus as a trinity. *J Dermatol Sci* 2013;70(1):3–11.
- Kwatra SG, Tey HL, Ali SM, et al. The infra-auricular fissure: a bedside marker of disease severity in patients with atopic dermatitis. *J Am Acad Dermatol* 2012;66(6):1009–10.
- Langan S, Williams HC. Clinical features and diagnostic criteria of atopic dermatitis. In: Irvine A, Hoeger P, Yan A, editors. *Textbook of pediatric dermatology*. 3rd ed. Oxford: Blackwell; 2011. p. 28.1–28.19.
- Williams HC, Burney PG, Hay RJ, et al. The UK Working Party's diagnostic criteria for atopic dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;131:383–96.
- Eichenfield LF, Hanifin JM, Luger TA, et al. Consensus conference on pediatric atopic dermatitis. *J Am Acad Dermatol* 2003;49:1088–95.
- Haileamlak A, Lewis SA, Britton J, et al. Validation of the International Study of Asthma and Allergies in Children (ISAAC) and U.K. criteria for atopic eczema in Ethiopian children. *Br J Dermatol* 2005;152:735–41.
- Kou K, Aihara M, Matsunaga T, et al. Association of serum interleukin-18 and other biomarkers with disease severity in adults with atopic dermatitis. *Arch Dermatol Res* 2012;304(4):305–12.
- Yosipovitch G, Papoiu AD. What causes itch in atopic dermatitis? *Curr Allergy Asthma Rep* 2008;8(4):306–11.
- Guttman-Yassky E, Nograles KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis – part I: clinical and pathologic concepts. *J Allergy Clin Immunol* 2011;127(5):1110–18.
- Wolf R, Wolf D. Abnormal epidermal barrier in the pathogenesis of atopic dermatitis. *Clin Dermatol* 2012;30(3):329–34.
- Schultz Larsen F. Atopic dermatitis: a genetic-epidemiologic study in a population-based twin sample. *J Am Acad Dermatol* 1993;28(5 Pt 1):719–23.
- Bellou A, Kanny G, Fremont S, et al. Transfer of atopy following bone marrow transplantation. *Ann Allergy Asthma Immunol* 1997;78:513–16.
- Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. *N Engl J Med* 2011;365(14):1315–27.
- Bussmann C, Weidinger S, Novak N. Genetics of atopic dermatitis. *J Dtsch Dermatol Ges* 2011;9(9):670–6.
- Barnes KC. An update on the genetics of atopic dermatitis: scratching the surface in 2009. *J Allergy Clin Immunol* 2010;125(1):16–29.e1–11; quiz 30–1.
- Sajić D, Asinwasis R, Skotnicki-Grant S. A look at epidermal barrier function in atopic dermatitis: physiologic lipid replacement and the role of ceramides. *Skin Therapy Lett* 2012;17(7):6–9.
- Lee J, Noh G, Lee S, et al. Atopic dermatitis and cytokines: recent patents in immunoregulatory and therapeutic implications of cytokines in atopic dermatitis – part I: cytokines in atopic dermatitis. *Recent Pat Inflamm Allergy Drug Discov* 2012;6(3):222–47.
- Souwer Y, Szegedi K, Kapsenberg ML, et al. IL-17 and IL-22 in atopic allergic disease. *Curr Opin Immunol* 2010;22(6):821–6.
- Mrabet-Dahbi S, Maurer M. Innate immunity in atopic dermatitis. *Curr Probl Dermatol* 2011;41:104–11.
- Lin YT, Wang CT, Chiang BL. Role of bacterial pathogens in atopic dermatitis. *Clin Rev Allergy Immunol* 2007;33(3):167–77.
- Eller E, Kjaer HF, Høst A, et al. Food allergy and food sensitization in early childhood: results from the DARC cohort. *Allergy* 2009;64(7):1023–9.
- Fuiano N, Incorvaia C. Dissecting the causes of atopic dermatitis in children: less foods, more mites. *Allergol Int* 2012;61(2):231–43.
- Buddenkotte J, Steinhoff M. Pathophysiology and therapy of pruritus in allergic and atopic diseases. *Allergy* 2010;65(7):805–21.
- Boguniewicz M, Leung DY. Atopic dermatitis: a disease of altered skin barrier and immune dysregulation. *Immunol Rev* 2011;242(1):233–46.
- Kapila S, Hong E, Fischer G. A comparative study of childhood psoriasis and atopic dermatitis and greater understanding of the overlapping condition, psoriasis-dermatitis. *Australas J Dermatol* 2012;53(2):98–105.
- Vickers CF. The natural history of atopic eczema. *Acta Derm Venereol (Stockh)* 1980;92(Suppl.):113–15.
- Wüthrich B. Clinical aspects, epidemiology, and prognosis of atopic dermatitis. *Ann Allergy Asthma Immunol* 1999;83(5):464–70.
- Williams HC, Strachan DP. The natural history of childhood eczema: observations from the British 1958 birth cohort study. *Br J Dermatol* 1998;139(5):834–9.
- Illi S, von Mutius E, Lau S, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004;113(5):925–31.
- Bingefors K, Svensson A, Isacson D, et al. Self-reported lifetime prevalence of atopic dermatitis and co-morbidity with asthma and eczema in adulthood: a population-based cross-sectional survey. *Acta Derm Venereol* 2013;93(4):438–41.
- Simpson EL. Comorbidity in Atopic Dermatitis. *Curr Dermatol Rep* 2012;1(1):29–38.
- Queille-Roussel C, Raynaud F, Saurat JH. A prospective computerized study of 500 cases of atopic dermatitis in childhood. I. Initial analysis of 250 parameters. *Acta Derm Venereol Suppl (Stockh)* 1985;114:87–92.

55. Ricci G, Patrizi A, Baldi E, et al. Long-term follow-up of atopic dermatitis: retrospective analysis of related risk factors and association with concomitant allergic diseases. *J Am Acad Dermatol* 2006;55(5):765–71.
56. Demehri S, Morimoto M, Holtzman MJ, et al. Skin-derived TSLP triggers progression from epidermal-barrier defects to asthma. *PLoS Biol* 2009;7(5):e1000067.
57. Barbarot S, Bernier C, Deleuran M, et al. Therapeutic patient education in children with atopic dermatitis: position paper on objectives and recommendations. *Pediatr Dermatol* 2013;30(2):199–206.
58. Robinson M, Visscher M, Laruffa A, et al. Natural moisturizing factors (NMF) in the stratum corneum (SC). II. Regeneration of NMF over time after soaking. *J Cosmet Sci* 2010;61(1):23–9.
59. Chiang C, Eichenfield LF. Quantitative assessment of combination bathing and moisturizing regimens on skin hydration in atopic dermatitis. *Pediatr Dermatol* 2009;26(3):273–8.
60. Gutman AB, Kligman AM, Sciacca J, et al. Soak and smear: a standard technique revisited. *Arch Dermatol* 2005;141(12):1556–9.
61. Lucky AW, Leach AD, Laskarzewski P, et al. Use of an emollient as a steroid-sparing agent in the treatment of mild to moderate atopic dermatitis in children. *Pediatr Dermatol* 1997;14(4):321–4.
62. Valdman-Grinshpoun Y, Ben-Amitai D, Zvulunov A. Barrier-restoring therapies in atopic dermatitis: current approaches and future perspectives. *Dermatol Res Pract* 2012;2012:923134.
63. Miller DW, Koch SB, Yentzer BA, et al. An over-the-counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: a randomized, controlled trial. *J Drugs Dermatol* 2011;10(5):531–7.
64. Charman C, Williams H. The use of corticosteroids and corticosteroid phobia in atopic dermatitis. *Clin Dermatol* 2003;21(3):193–200.
65. Callen J, Chamlin S, Eichenfield LF, et al. A systematic review of the safety of topical therapies for atopic dermatitis. *Br J Dermatol* 2007;156(2):203–21.
66. Eichenfield LF. Consensus guidelines in diagnosis and treatment of atopic dermatitis. *Allergy* 2004;59(Suppl. 78):86–92.
67. Devillers AC, Oranje AP. Wet-wrap treatment in children with atopic dermatitis: a practical guideline. *Pediatr Dermatol* 2012;29(1):24–7.
68. Kalavala M, Mills CM, Long CC, et al. The fingertip unit: A practical guide to topical therapy in children. *J Dermatol Treat* 2007;18(5):319–20.
69. Jensen JM, Pfeiffer S, Witt M, et al. Different effects of pimecrolimus and betamethasone on the skin barrier in patients with atopic dermatitis. *J Allergy Clin Immunol* 2009;123(5):1124–33.
70. Paul C, Cork M, Rossi AB, et al. Safety and tolerability of 1% pimecrolimus cream among infants: experience with 1133 patients treated for up to 2 years. *Pediatrics* 2006;117(1):e118–e128.
71. Kalavala M, Dohil MA. Calcineurin inhibitors in pediatric atopic dermatitis: a review of current evidence. *Am J Clin Dermatol* 2011;12(1):15–24.
72. Ohtsuki M, Ohara H, Santos V, et al. Safety profiles of two large cohort studies of tacrolimus ointment for the treatment of atopic dermatitis: A prospective pediatric longitudinal evaluation study (APPLES) and Japanese long-term safety study (J-LSS). Poster presented at the 22nd World Congress of Dermatology; May 24–9, 2011, Seoul, Korea.
73. Paller AS, Michaels MA, Bieber T. Assessing the long-term safety of tacrolimus ointment for the treatment of atopic dermatitis: An update on a prospective pediatric longitudinal evaluation study (APPLES). *J Am Acad Dermatol* 2010;62(3)Suppl. 1:AB10.
74. Arellano FM, Wentworth CE, Arana A, et al. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol* 2007;127(4):808–16.
75. Paller AS, Simpson EL, Eichenfield LF, et al. Treatment strategies for atopic dermatitis: optimizing the available therapeutic options. *Semin Cutan Med Surg* 2012;31(Suppl. 3):S10–17.
76. Wollenberg A, Ehmann LM. Long term treatment concepts and proactive therapy for atopic eczema. *Ann Dermatol* 2012;24(3):253–60.
77. Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000;4(37):1–191.
78. Darso U, Wollenberg A, Simon D, et al. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. *Eur Acad Dermatol Venereol* 2010;24(3):317–28.
79. Vlachou C, Thomas KS, Williams HC. A case report and critical appraisal of the literature on the use of DermaSilk in children with atopic dermatitis. *Clin Exp Dermatol* 2009;34:e901–3.
80. Dai YS. Allergens in atopic dermatitis. *Clin Rev Allergy Immunol* 2007;33(3):157–66.
81. Nilsson EJ, Henning CG, Magnusson J. Topical corticosteroids and *Staphylococcus aureus* in atopic dermatitis. *J Am Acad Dermatol* 1992;27:29–34.
82. Bath-Hextall FJ, Birnie AJ, Ravenscroft JC, et al. Interventions to reduce *Staphylococcus aureus* in the management of atopic eczema: an updated Cochrane review. *Br J Dermatol* 2010;163(1):12–26.
83. Balma-Mena A, Lara-Corrales I, Zeller J, et al. Colonization with community-acquired methicillin-resistant *Staphylococcus aureus* in children with atopic dermatitis: a cross-sectional study. *Int J Dermatol* 2011;50(6):682–8.
84. Matiz C, Tom WL, Eichenfield LF, et al. Children with atopic dermatitis appear less likely to be infected with community acquired methicillin-resistant *Staphylococcus aureus*: the San Diego experience. *Pediatr Dermatol* 2011;28(1):6–11.
85. Huang JT, Abrams M, Tloughan B, et al. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics* 2009;123(5):e808–14.
86. Jen M, Chang MW. Eczema herpeticum and eczema vaccinatum in children. *Pediatr Ann* 2010;39(10):658–64.
87. Kennedy JS, Greenberg RN. IMVAMUNE: modified vaccinia Ankara strain as an attenuated smallpox vaccine. *Expert Rev Vaccines* 2009;8(1):13–24.
88. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-Sponsored Expert Panel report. *J Am Acad Dermatol* 2011;64(1):175–92.
89. Simpson EL, Eichenfield LF, Ellis CN, et al. Current issues in atopic comorbidities and preventing the atopic march. *Semin Cutan Med Surg* 2012;31(Suppl. 3):S6–9.
90. Keller MD, Shuker M, Heimall J, et al. Severe malnutrition resulting from use of rice milk in food elimination diets for atopic dermatitis. *Isr Med Assoc J* 2012;14(1):40–2.
91. Eisenberger D, Davis R, Ettner S, et al. Trends in alternative medicine in the United States 1990–1997. *JAMA* 1998;18:1569–1575.
92. Koo J, Arain S. Traditional Chinese medicine for the treatment of dermatologic disorders. *Arch Dermatol* 1998;134(11):1388–93.
93. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012;26(9):1176–93.
94. Osborn DA, Sinn JK. Probiotics in infants for prevention of allergic disease and food hypersensitivity. *Cochrane Database Syst Rev* 2007;(4):CD006475.
95. Greer FR, Sicherer SH, Burks AW. American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121(1):183–91.
96. Foisy M, Boyle RJ, Chalmers JR, et al. Overview of reviews. The prevention of eczema in infants and children: an overview of Cochrane and non-Cochrane reviews. *Evid Based Child Health* 2011;6(5):1322–39.
97. Simpson EL, Berry TM, Brown PA, et al. A pilot study of emollient therapy for the primary prevention of atopic dermatitis. *J Am Acad Dermatol* 2010;63(4):587–93.
98. Foley P, Zuo Y, Plunkett A, et al. The frequency of common skin conditions in preschool-aged children in Australia: seborrheic dermatitis and pityriasis capitis (cradle cap). *Arch Dermatol* 2003;139(3):318–22.
99. Schwartz RA, Janusz CA, Janniger CK. Seborrheic dermatitis: an overview. *Am Fam Physician* 2006;74(1):125–30.
100. Gupta AK, Madzia SE, Batra R. Etiology and management of seborrheic dermatitis. *Dermatology* 2004;208(2):89–93.
101. Williams JV, Eichenfield LF, Burke BL, et al. Prevalence of scalp scaling in prepubertal children. *Pediatrics* 2005;115(1):e1–6.
102. Ale IS, Maibach HA. Diagnostic approach in allergic and irritant contact dermatitis. *Expert Rev Clin Immunol* 2010;6(2):291–310.
103. Atherton DJ. A review of the pathophysiology, prevention and treatment of irritant diaper dermatitis. *Curr Med Res Opin* 2004;20(5):645–9.
104. Fleischer AB Jr. Diagnosis and management of common dermatoses in children: atopic, seborrheic, and contact dermatitis. *Clin Pediatr (Phila)* 2008;47(4):332–46.
105. Smith WA, Taintor AR, Kos L, et al. Senna-containing laxative inducing blistering dermatitis in toddlers. *Arch Dermatol* 2012;148(3):402–4.
106. Eberhard Y, Ortiz S, Ruiz Lascano A, et al. Up-regulation of the chemokine CCL21 in the

- skin of subjects exposed to irritants. *BMC Immunol* 2004;5:7.
107. Ravanfar P, Wallace JS, Pace NC. Diaper dermatitis: a review and update. *Curr Opin Pediatr* 2012;24(4):472–9.
 108. Belloni Fortina A, Romano I, Peserico A, et al. Contact sensitization in very young children. *J Am Acad Dermatol* 2011;65(4):772–9.
 109. Thyssen JP, Johansen JD, Linneberg A, et al. The association between null mutations in the filaggrin gene and contact sensitization to nickel and other chemicals in the general population. *Br J Dermatol* 2010;162(6):1278–85.
 110. Ghali FE. 'Car seat dermatitis': a newly described form of contact dermatitis. *Pediatr Dermatol* 2011;28(3):321–6.
 111. Simonsen AB, Deleuran M, Johansen JD, et al. Contact allergy and allergic contact dermatitis in children – a review of current data. *Contact Dermatitis* 2011;65(5):254–65.
 112. Jacob SE, Steele T, Brod B, et al. Dispelling the myths behind pediatric patch testing: experience from our tertiary care patch testing centers. *Pediatr Dermatol* 2008;25(3):296–300.
 113. Gehrig KA, Dinulos JG. Acrodermatitis due to nutritional deficiency. *Curr Opin Pediatr* 2010;22(1):107–12.
 114. Lonnerdal B, Stanislawski AG, Hurley LS. Isolation of a low molecular weight zinc binding ligand from human milk. *J Inorg Biochem* 1980;12:71–8.
 115. Chohanadisai W, Lönnerdal B, Kelleher SL. Identification of a mutation in SLC30A2 (ZnT-2) in women with low milk zinc concentration that results in transient neonatal zinc deficiency. *J Biol Chem* 2006;281(51):39699–707.
 116. Van Wouwe JP. Clinical and laboratory diagnosis of acrodermatitis enteropathica. *Eur J Pediatr* 1989;149:2–8.
 117. Goskowitz M, Eichenfield LF. Cutaneous findings of nutritional deficiencies in children. *Curr Opin Pediatr* 1993;5(4):441–5.
 118. Cowan TM, Blitzer MG, Wolf B. Working Group of the American College of Medical Genetics Laboratory Quality Assurance Committee. Technical standards and guidelines for the diagnosis of biotinidase deficiency. *Genet Med* 2010;12(7):464–70.
 119. Darmstadt GL, Schmidt CP, Wechsler DS, et al. Dermatitis as a presenting sign of cystic fibrosis. *Arch Dermatol* 1992;128(10):1358–64.
 120. Condren ME, Bradshaw MD. Ivacaftor: a novel gene-based therapeutic approach for cystic fibrosis. *J Pediatr Pharmacol Ther* 2013;18(1):8–13.
 121. Wilcken B, Yu JS, Brown DA. Natural history of Hartnup disease. *Arch Dis Child* 1977;52(1):38–40.
 122. Lee EB. Metabolic diseases and the skin. *Pediatr Clin North Am* 1983;30(4):597–608.
 123. Keil S, Anjema K, van Spronsen FJ, et al. Long-term Follow-up and Outcome of Phenylketonuria Patients on Sapropterin: A Retrospective Study. *Pediatrics* 2013;131(6):e1881–8.
 124. D'Alessio M, Fortugno P, Zambruno G, et al. Netherton syndrome and its multifaceted defective protein LEKTI. *G Ital Dermatol Venereol* 2013;148(1):37–51.
 125. Oji V, Traupe H. Ichthyosis: clinical manifestations and practical treatment options. *Am J Clin Dermatol* 2009;10(6):351–64.
 126. Sponzilli I, Notarangelo LD. Severe combined immunodeficiency (SCID): from molecular basis to clinical management. *Acta Biomed* 2011;82(1):5–13.
 127. Sillevius Smitt JH, Kuijpers TW. Cutaneous manifestations of primary immunodeficiency. *Curr Opin Pediatr* 2013;25(4):492–7.
 128. Al-Herz W, Nanda A. Skin manifestations in primary immunodeficient children. *Pediatr Dermatol* 2011;28(5):494–501.
 129. Ariga T. Wiskott-Aldrich syndrome; an x-linked primary immunodeficiency disease with unique and characteristic features. *Allergol Int* 2012;61(2):183–9.
 130. Yong PF, Freeman AF, Engelhardt KR, et al. An update on the hyper-IgE syndromes. *Arthritis Res Ther* 2012;14(6):228.
 131. Freeman AF, Holland SM. Clinical manifestations of hyper-IgE syndromes. *Dis Markers* 2010;29(3–4):123–30.
 132. Freeman AF, Avila EM, Shaw PA, et al. Coronary artery abnormalities in hyper-IgE syndrome. *J Clin Immunol* 2011;31(3):338–45.
 133. Chu EY, Freeman AF, Jing H, et al. Cutaneous manifestations of DOCK-8 deficiency syndrome. *Arch Dermatol* 2012;148(1):79–84.

Papulosquamous and Lichenoid Disorders

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Papulosquamous disorders

PSORIASIS

Introduction

Psoriasis is a chronic, inflammatory papulosquamous disease with an estimated prevalence of 1% in children.¹ Pediatric psoriasis is subdivided into congenital, infantile, and childhood, defined as psoriasis presenting at birth, in the first year of life, and between ages 1 and 18 years, respectively. One-third of all patients develop psoriasis in the first two decades of life. Up to 30% of these patients manifest by age 2 with psoriatic diaper rash.²⁻⁴ Age of onset may predict disease severity. In a large cohort study of childhood psoriasis, for every year increase in age of onset from birth to 18 years, there was a 10% decrease in risk of moderate–severe disease.⁵ Precipitating factors are more common in childhood compared with adult-onset psoriasis. Trauma (via Koebner phenomenon) and infections (pharyngeal and perianal group A streptococci in particular) are frequently implicated in initiation and exacerbation of early-onset psoriasis.⁶ Psoriasis arising during the acute and convalescent phases of Kawasaki disease has been reported in infants as young as 3 months.⁷

While psoriasis is diagnosed by the presence of characteristic clinical features, diagnosis in the neonatal and infantile period can be challenging because of clinical overlap with other common papulosquamous eruptions. A skin biopsy may be required to confirm the diagnosis in severe or worrisome cases. Otherwise, tincture of time often illuminates the correct diagnosis as the disease evolves towards more classic features.

Cutaneous findings

Plaque and guttate psoriasis are the most common morphologies observed in children. Individual lesions of typical psoriasis consist of erythematous, well-demarcated plaques with silvery-white scale. Guttate, or ‘drop-like’ psoriasis is an eruption of individual papules and small plaques up to 1 cm in size (Fig. 16.1). Psoriasis in infants offers unique variations of morphology and distribution. For example, annular and serpiginous patterns are common (Fig. 16.2) and involvement of the face and anogenital region is typical (Fig. 16.3). Scale may be imperceptible in psoriasis arising in the diaper area, folds and flexures. The Koebner phenomenon (isomorphic response or psoriasis arising at sites of trauma) is commonly observed and may explain the common distributions of psoriasis in the diaper area, scalp and face of infants, as opposed to adults (Fig. 16.4). Nail changes are present in 10% of infants with psoriasis and may include pitting, onycholysis, oil spots, and subungual hyperkeratosis. Pruritus is common. Box 16.1

summarizes the clinical variants and distributions of psoriasis in children.

Diaper psoriasis. In children younger than 2 years of age, psoriatic diaper rash is a common presentation (see also Chapter 17). It presents as bright red, glazed appearing, well-margined individual or confluent plaques with absent or minimal scale, involving the anogenital area including skin folds. It often expands toward the abdomen and thighs where the scale becomes more perceptible (Fig. 16.5). In some cases, there is widespread dissemination of the psoriasis shortly after the diaper eruption appears, referred to as psoriatic diaper rash with dissemination or as diaper dermatitis with psoriasiform id reaction (Fig. 16.6).⁸ Psoriasis and other acute diaper rashes, such as *Candida*, may result in a psoriasiform id reaction (Fig. 16.7). The initial stages of diaper (‘napkin’) psoriasis are easily confused with other diaper rashes, including irritant dermatitis (which typically spares the folds), *Candida* infection, seborrheic dermatitis as well as other causes. Infants with diaper psoriasis with dissemination of lesions to other areas of the body and a positive first-degree family history of psoriasis are probably at greatest risk for developing typical psoriasis later in life.⁹⁻¹¹

Treatment consists of bland emollients and topical anti-inflammatory agents used in combination. Ointment formulations tend to have greater efficacy and tolerability (i.e., less burning with application) than creams. Effective agents include low to mid-potency topical steroids, topical calcineurin inhibitors, low concentrations of liquor carbonis detergens (3–5% LCD) compounded in either white petrolatum or low potency topical steroid, and topical vitamin D analogs such as calcitriol or calcipotriene.

Erythrodermic psoriasis. Psoriasis presenting as congenital or neonatal erythroderma is a rare, but documented, presentation.^{12,13} Neonatal erythrodermic psoriasis has overlapping features with primary immunodeficiency syndromes, Netherton syndrome, metabolic disorders, systemic infections, and certain forms of ichthyosis. A positive family history of psoriasis, patchy rather than diffuse involvement, and absence of other features of ichthyosis (e.g., ectropion and eclabium) may help to differentiate psoriasis from ichthyosis in early life.¹⁴ The prognosis is guarded. Evolution over time often results in typical localized psoriatic plaques or the erythroderma may persist.¹² This presentation is also potentially life-threatening. The impaired skin barrier confers a risk of hyperpyrexia, hypernatremic dehydration, hypoalbuminemia, septicemia, and cutaneous infections. Management consists of optimized nutritional status and fluid and electrolyte balance. Control of inflammation with topical steroids and barrier reinforcement with bland



Figure 16.4 Severe facial and scalp psoriasis. (A) Infant and (B) 3-year-old child.



Figure 16.5 Diaper psoriasis spreading to thighs and abdomen.



Figure 16.7 A 19-month-old child with *Candida* diaper dermatitis with widespread psoriasiform id reaction. (A) Diaper area. (B) Posterior neck.



Figure 16.1 Infant with guttate psoriasis.



Figure 16.2 Annular psoriasis on the arm of an infant. (Reproduced with permission from Cordoro KM. *Management of childhood psoriasis*. *Adv Dermatol* 2008; 24:125–169.)

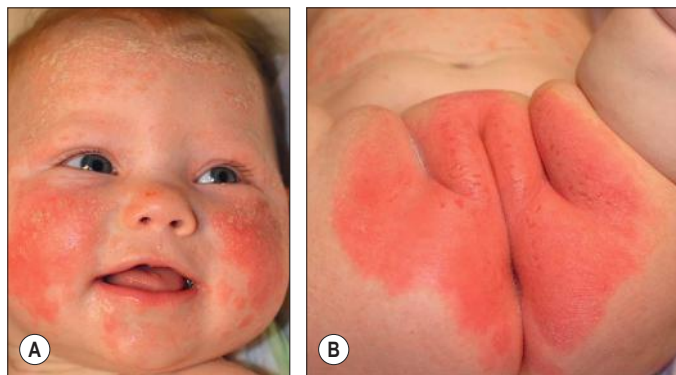


Figure 16.3 Psoriasis with: (A) Facial and (B) anogenital involvement; this infant also has guttate psoriasis (see Fig. 16.1).

emollients to prevent further metabolic disarray and infections is imperative.

Pustular psoriasis. Pustular psoriasis in infancy may be localized or generalized. Generalized pustular psoriasis of von Zumbusch (GPP) is characterized by fever and an explosive eruption of sheets of sterile pustules on inflamed skin (Fig. 16.8). The pustules may be arranged at the periphery of annular or serpiginous plaques (Fig. 16.9). Annular pustular psoriasis, alone or together with generalized pustulation, is the most common form observed in children. Affected children may appear well or exhibit systemic symptoms of progressive malaise, lethargy,

BOX 16.1 CLINICAL VARIANTS AND DISTRIBUTIONS OF PSORIASIS IN CHILDREN

- Plaque: most frequent subtype, may be annular/figurate/arcuate/serpiginous
- Guttate
- Eczema-psoriasis overlap (eczematous psoriasis or psoriasiform eczema)
- Papular or follicular
- Scalp: localized or diffuse plaque, pityriasis amiantacea, dermatitis erythema nuchae
- Inverse: face and flexures, intertriginous
- Facial: periorbital, perioral, angular cheilitis
- Nails: pits, oil drops, onycholysis, subungual hyperkeratosis
- Linear/Blaschkoid
- Psoriatic diaper rash with or without dissemination
- Palmoplantar, interdigital web spaces
- Psoriatic arthropathy
- Pustular
 - Localized:
 - Acrodermatitis continua of Hallopeau (digits and nails)
 - Palmoplantar pustulosis
 - Plaque psoriasis studded with surface pustules
 - Generalized:
 - von Zumbusch (more common in infancy)
 - Annular variant with peripheral pustules (common in older children)
- Erythrodermic

Adapted from Cordoro KM. Management of childhood psoriasis. Adv Dermatol 2008; 24:125–169.



Figure 16.6 Diaper psoriasis with dissemination.

irritability and unwillingness to eat. GPP runs an unpredictable course with relapses and remissions. Severe, localized pustular psoriasis of the nail unit (acrodermatitis continua of Hallopeau) may occur in isolation or accompany generalized pustular psoriasis.

Pustular psoriasis localized to the intertriginous areas, particularly the neck, is a relatively uncommon subtype that may be misdiagnosed as bacterial or candidal intertrigo. Affected infants are often 1–2 months old and otherwise well. There may be a positive family history of psoriasis. This localized intertriginous variant may progress to widespread disease requiring systemic therapy.¹⁵



Figure 16.8 Generalized pustular psoriasis. (A) Infant. (B) Older child with confluence of pustules into lakes of pus. (A: Courtesy of Dr Brandon Newell.)



Figure 16.9 Annular pustular psoriasis in a young male child. (Reproduced with permission from Cordoro KM. Management of childhood psoriasis. *Adv Dermatol* 2008; 24:125–169.)

The differential diagnosis of neonatal and infantile pustulosis includes a recently described rare condition, ‘deficiency of interleukin 1 receptor antagonist’ (DIRA). DIRA is an autosomal recessive, early-onset, life-threatening autoinflammatory syndrome primarily affecting the skin and bones. Patients typically present as neonates or young infants with a localized or generalized pustular eruption, desquamation, multifocal osteomyelitis and periostitis, failure to thrive, and elevated inflammatory markers (Fig. 16.10).¹⁶ DIRA is mediated by mutations in the IL1RN gene encoding the interleukin 1 (IL-1) receptor antagonist, resulting in unopposed, widespread systemic inflammation. The allele frequencies of the causative mutations are highest in patients from Puerto Rico, the Netherlands, and Newfoundland. IL1RN gene sequencing is diagnostic. These patients require targeted therapy with the recombinant human IL-1 receptor antagonist, anakinra.^{16,17}

Other entities in the differential diagnosis of pustular psoriasis include: viral, fungal, and bacterial infections; secondarily

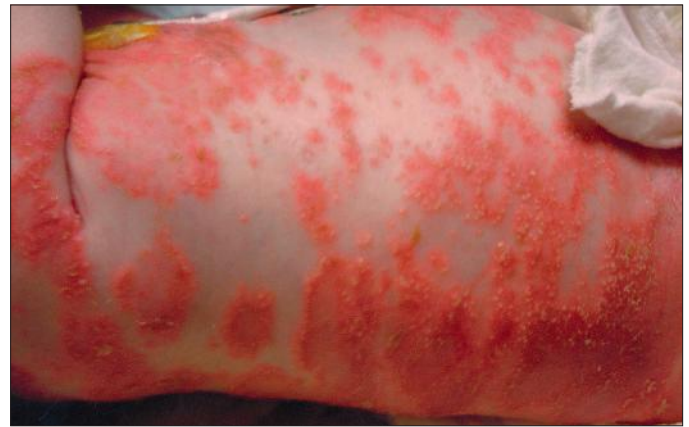


Figure 16.10 Pustular eruption in an infant with DIRA. (Courtesy of Dr Edward Cowen.)

infected atopic or seborrheic dermatitis; acute generalized exanthematous pustulosis; pityriasis rubra pilaris; scabies; miliaria; acrodermatitis enteropathica; eosinophilic pustular folliculitis; erythema toxicum neonatorum; the pustular leukemoid reaction associated with Trisomy 21; and transient neonatal pustular melanosis.

The treatment of GPP varies. Milder cases can be controlled with topical corticosteroids and vitamin D analogs. Severe cases may require hospitalization for work-up, supportive care and initiation of systemic therapy. Cultures should be obtained from pustular lesions, and if repeatedly sterile, should alert physicians to the diagnosis of pustular psoriasis. Oral retinoids, cyclosporine, methotrexate and phototherapy comprise the most commonly used and effective agents for severe, refractory or multiply-relapsed pustular psoriasis. Older children with disease refractory to traditional systemic medications may respond to anti-TNF therapy.¹⁸

Congenital psoriasis. Psoriasis presenting at birth is very rare. Only nine published cases of congenital psoriasis are diagnostically convincing. Of those, plaque, erythrodermic and pustular were the most common clinical subtypes observed. Although no consistent anatomic distribution has been distinguished, the scalp, face, extremities and trunk are commonly involved. Notably, the diaper area is frequently spared, perhaps due to lack of trauma from diapers.¹⁹ Histologically confirmed congenital psoriasis occurring along Blaschko's lines has been reported. Females are more frequently affected with Blaschkolinear psoriasis presumably due to functional X-chromosome mosaicism.²⁰ A maternal and family history of psoriasis is often absent in cases of congenital psoriasis.¹⁹

The differential diagnosis of congenital psoriasis depends on the presentation. Erythrodermic and papulosquamous cases should be distinguished from seborrheic dermatitis, including localized ‘cradle cap’, congenital or neonatal candidiasis, immunodeficiency syndromes, congenital ichthyosis and Netherton syndrome.²¹ Linear psoriasis must be differentiated from inflammatory linear verrucous epidermal nevi.²² The differential diagnosis for congenital pustular psoriasis includes: bacterial infections; candidiasis; erythema toxicum neonatorum; pustular leukemoid reaction in children with Trisomy 21; transient neonatal pustular melanosis; Langerhans' cell histiocytosis; and deficiency of interleukin 1 receptor antagonist (DIRA,

see above). Alternatively, congenital psoriasis should always be considered in the differential diagnosis of newborns with erythroderma, or papulosquamous or pustular eruptions.

Treatment for congenital psoriasis should be conservative initially with bland emollients and topical steroids. A 'soak and seal' regimen using wet wraps with low potency topical steroids can enhance efficacy. Systemic therapy with acitretin or methotrexate is required in some cases. Response to therapy is variable and depends on disease severity.

Long-term prognosis of congenital psoriasis is unknown because follow-up is unavailable for most cases. Infants with presumed pustular psoriasis, failure to thrive, skeletal anomalies and systemic symptoms who are refractory to therapy should be evaluated for DIRA.

Extracutaneous findings of infantile psoriasis

Pustular and erythrodermic psoriasis may be accompanied by systemic signs including fever, chills, irritability, lethargy, dehydration, and fluid and electrolyte imbalance, as discussed previously. Psoriatic arthritis is the most common comorbid association in childhood psoriasis but is infrequent in infants. Nail pitting, dactylitis, and enthesitis may be markers of children at risk for arthritis.²³ There is evidence that children with psoriasis, regardless of severity, are more likely to be overweight or obese and thus at increased risk for related complications.²⁴ A potential relationship between pediatric psoriasis and the metabolic syndrome requires further investigation.²⁵ At present, there are no data linking infantile psoriasis with obesity or metabolic syndrome.

Differential diagnosis

The differential diagnosis depends on the specific morphology and distribution. Scalp psoriasis may resemble seborrheic or atopic dermatitis in infants. Tinea capitis more frequently has alopecia or hair breakage and can be distinguished with fungal culture. Plaque and guttate psoriasis must be differentiated from neonatal lupus, pityriasis alba, nummular atopic dermatitis, pityriasis rosea, pityriasis rubra pilaris, and tinea corporis. Atopic dermatitis is usually associated with significantly more pruritus and often with other atopic stigmata or family history. Possible infectious etiologies must be considered in pustular psoriasis. Kawasaki disease may display psoriasis-like eruptions in infants, but has other characteristic features which can aid in diagnosis.

Etiology and pathogenesis

Psoriasis is an immune-mediated inflammatory disease that results in accelerated epidermal cell turnover observed clinically as scaly red plaques. The dysregulated cutaneous immune response is modified by environmental factors in genetically susceptible individuals.²⁶ Psoriasis following bacterial infections as well as Kawasaki disease suggests the potential pathogenic role of superantigens.^{27,28} A family history of psoriasis is often absent in infantile cases but the rate climbs to 80% in older children.²⁴ HLA-Cw6 is the major risk allele that confers susceptibility to early-onset psoriasis.²⁹

Characteristic histology of plaque psoriasis includes parakeratosis, loss of the granular layer, Munro microabscesses, spongiform pustules of Kogoj and a dermal lymphocytic infiltrate. Pustular psoriasis features intraepidermal subcorneal pustules and a mixed dermal inflammatory infiltrate.

Treatment and prognosis

As a chronic disease, psoriasis is characterized by intermittent exacerbations and spontaneous remissions. The choice of treatment is determined by disease morphology, distribution, severity, comorbidities and patient age. Conservative management with cautious progression to systemic therapies in critical cases is recommended for infantile psoriasis. Topical therapies including bland emollients, corticosteroids, vitamin D analogs, topical calcineurin inhibitors, anthralin and tar-based preparations (liquor carbonis detergens 3–5%) may be tried initially and are often all that is necessary for thin plaque or guttate psoriasis.

Severe or rapidly progressive disease refractory to combination topical therapy may require systemic therapy with retinoids, cyclosporine, methotrexate or conservative doses of narrow band UVB phototherapy. Systemic agents require close clinical and laboratory monitoring. Table 16.1 reviews the various topical therapies and Table 16.2 the systemic agents available to treat childhood psoriasis. Comprehensive reviews of management principles for pediatric psoriasis have been recently published.^{5,30}

The prognosis of the various forms of infantile psoriasis is variable and requires further study. A positive family history of psoriasis and initial presentation with guttate morphology may predict more severe plaque psoriasis later in life.³¹

PITYRIASIS RUBRA PILARIS

Introduction

Pityriasis rubra pilaris (PRP) is a papulosquamous disorder of unknown etiology. The age of onset is bimodal, with peaks in the first and fifth decades of life. Reports of PRP in children less than 2 years old date back to 1905.³² Griffiths originally classified patients with PRP into five types based on clinical features, age of onset and prognosis. Type I and II are adult-onset forms (classic and atypical, respectively) and types III, IV, and V represent the juvenile-onset spectrum.³³ Each juvenile type of PRP may arise in infancy and early childhood (see Table 16.3).

Type III classic juvenile PRP and type IV circumscribed juvenile PRP are more common in older children but can occur early in life. An acute post-infectious form of PRP, which has similar morphologic features to type III, has been observed in infants and young children.^{34,35} Type V atypical juvenile PRP may be congenital or develop within the first few years.^{33,36} A positive family history of PRP is reported in up to 6.5% of patients. These rare familial cases are typically inherited in autosomal dominant fashion and fit clinically into type V.^{37,38} Griffiths surmised that more than one disease is probably represented in some cases designated as type V PRP, including forms of congenital follicular ichthyosis.³³

Cutaneous findings

There is considerable heterogeneity and overlap of clinical features among the various types of PRP in children (Table 16.3). The classic findings of PRP are follicular hyperkeratosis, scattered salmon-colored scaly patches and plaques, varying degrees of erythroderma, and palmoplantar keratoderma. Though the classic primary lesion of PRP is a follicular keratotic papule, this is not universally observed. Neonates and infants may present with erythroderma.³⁹ Diagnosis is based on distinctive clinical features and supportive histopathology.

TABLE
16.2

Systemic agents for psoriasis and suggested monitoring

Drug	Mechanism of action	Dosing	Baseline	Follow-up	Miscellaneous
Methotrexate (MTX)	Folic acid analog, inhibits DHFR and interferes with DNA synthesis and effects on T cells	0.2–0.7 mg/kg per week Start with test dose 1.25–5 mg; then increase by 1.25–5 mg per week until therapeutic effect obtained	CBC/platelets Liver function Renal function Hepatitis A/B/C HIV if at risk	CBC, platelets, liver function 7 days after test dose, then: weekly for 2–4 weeks and after each dose, then every 2 weeks for 1 month and every 2–3 months while on stable doses Renal function every 6–12 months	Liver enzymes transiently rise after MTX dosing; obtain labs 5–7 days after the last dose Liver biopsy: no standard recommendations. Avoid in children with or at risk for liver disease CXR if respiratory symptoms arise
Retinoids (acitretin)	Vitamin-A analog, binds to nuclear receptors and affects cellular metabolism, epidermal differentiation and apoptosis	0.5–1 mg/kg per day	CBC/platelets Liver function Renal function Fasting lipid profile Pregnancy testing if appropriate	Liver function and lipid profile after 1 month of treatment and with dose increases, then every 3 months Monthly pregnancy test (if age appropriate)	Baseline skeletal survey if long-term treatment anticipated: X-rays of all four limbs and spine, repeated yearly or if symptomatic Ophthalmologic examination if symptomatic
Cyclosporine	Calcineurin inhibitor, specifically and reversibly inhibits immunocompetent T cells and suppresses proinflammatory cytokines IL-2 and IFN γ	3–5+ mg/kg per day	Blood pressure \times 2 Renal function Urinalysis with micro fasting lipid profile CBC/platelets Liver function Magnesium Potassium Uric acid HIV if at risk	Blood pressure every visit Every 2 weeks for 1–2 months, then monthly: renal function, liver function, lipids, CBC, Mg $^{+}$, K $^{+}$, uric acid	Whole-blood CSA trough level if inadequate clinical response or concomitant use of potentially interacting medications. If Cr increases >25% above baseline, reduce dose by 1 mg/kg per day for 2–4 weeks and re-check. Stop CSA if Cr remains >25% above baseline; hold lower dose if level is within 25% of baseline
Biologics TNF α inhibitors Etanercept Infliximab Adalimumab	Etanercept: Fully human fusion protein of TNF α receptor II bound to the Fc component of human IgG1 Infliximab/ Adalimumab: monoclonal antibodies bind TNF α	Etanercept: 0.8 mg/kg SC weekly or 0.4 mg/kg BIW Infliximab: 3.3–5 mg/kg IV at weeks 0, 2, 6, then q 7–8 weeks Adalimumab: 24 mg/m 2 SC (max 40 mg) q 2 weeks ^a	PPD Electrolytes Liver function CBC with differential Hepatitis A/B/C if at risk HIV if at risk Update vaccinations	CBC, liver function every 4–6 months. Liver function more frequently with infliximab PPD annually Other labs/serologies per signs and symptoms	Avoid live and live-attenuated vaccines (e.g., varicella; MMR; oral typhoid; yellow fever; intranasal influenza; herpes zoster; BCG). Vaccinate household contacts prior to treatment initiation

CBC, complete blood count; Cr, creatinine; CSA, cyclosporine; CXR, chest X-ray; MTX, methotrexate; TNF α , tumor necrosis factor alpha; IL-2, interleukin-2; IFN γ , interferon-gamma; PPD, purified protein derivative; MMR, measles-mumps-rubella vaccine; BCG, Bacillus Calmette–Guérin; BIW, twice weekly.

^aDosing from published experience in patients with juvenile idiopathic arthritis; in two case reports in pediatric psoriasis, dosing was 40 mg q 2 weeks in two adolescent patients.

Adapted from Cordoro KM. Management of childhood psoriasis. *Adv Dermatol* 2008; 24:125–169; and Marqueling AL, Cordoro KM. Systemic treatments for severe pediatric psoriasis: a practical approach. *Dermatol Clin* 2013; 31:267–288.

TABLE
16.3

Major types of pityriasis rubra pilaris that present in infants or neonates

Type	Clinical features	Notes
III classic juvenile	May present as erythroderma. Whitish flaky scale on face and scalp. Follicular keratotic papules and scaly red patches spread cephalocaudally; may develop salmon colored erythroderma admixed with foci of normal skin. Most have palmoplantar keratoderma	May present in first few years of life Over time, the follicular component may be lost and lesions appear more like psoriasis Ectropion in severe cases
IV circumscribed juvenile	Well-demarcated plaques on elbows, knees, ankles, dorsal hands and feet. Some have palmoplantar keratoderma	Most common in pre-adolescents but can present in first few years of life
V atypical juvenile	Follicular hyperkeratosis, erythema and ichthyosiform dermatitis. Sclerodermoid appearance of hands and feet; may develop contractures	May be congenital and familial. May arise in first few years of life
Acute post-infectious	Initially resembles superantigen-mediated disease followed by classic features similar to type III	Infants and young children. Follows infection

TABLE 16.1 Selected topical therapies for childhood psoriasis

Medication	Mechanism of action	Clinical utility	Potential adverse effects
Corticosteroids	Anti-inflammatory and antiproliferative	All psoriasis variants; all sites of involvement (vary potency and frequency according to site of application (see text))	Skin atrophy, striae, secondary infection, systemic absorption and HPA axis suppression if diffuse, prolonged application of potent agents
Anthralin (dithranol)	Anti-inflammatory and antiproliferative	Plaque psoriasis Guttate psoriasis Nail psoriasis	Staining, irritation, contact dermatitis. Do not use on face or for erythrodermic or pustular psoriasis
Coal tar/LCD ^a	Largely unknown Enzyme inhibition and antimitotic actions; suppression of DNA synthesis	Plaque psoriasis Guttate psoriasis Inverse psoriasis Palmoplantar psoriasis	Folliculitis, irritant/allergic contact dermatitis, photosensitivity; pustular or erythrodermic reactions if used on acutely inflamed psoriasis. Do not use on inflamed, erythrodermic or generalized pustular psoriasis
Calcipotriene Calcipotriol	Stimulates epidermal differentiation and inhibits epidermal proliferation	Plaque psoriasis Guttate psoriasis Nail psoriasis Pustular psoriasis Inverse (calcipotriol) Scalp psoriasis	Irritation, hypercalcemia in excessive dosages
Tazarotene	Restores normal epidermal differentiation and proliferation and reduces epidermal inflammation	Thick plaque psoriasis Palmoplantar psoriasis Nail psoriasis	Irritation, teratogenicity (pregnancy category X)
Calcineurin inhibitors: Tacrolimus Pimecrolimus	Inhibit production of IL-2 and subsequent T-cell activation/proliferation	Thin plaque psoriasis Guttate psoriasis Facial psoriasis Eyelid psoriasis Intertriginous psoriasis Anogenital psoriasis	Skin stinging and pruritus FDA advises (for dermatitis). Avoid in children <2 years (pimecrolimus and tacrolimus 0.03% and 0.1%); and children <15 years old (tacrolimus 0.1%)

^aLiquor carbonis detergens.Adapted from Cordoro KM. Management of childhood psoriasis. *Adv Dermatol* 2008; 24:125–169.

Type III classic juvenile PRP often starts on the face and scalp with fine, whitish, powdery scale. The upper trunk develops an eruption of follicular hyperkeratotic papules that coalesce and progress in a cephalocaudal direction towards generalized erythroderma with islands of sparing (Figs 16.11A–C, 16.12). The erythroderma is orange-yellow, salmon, or red-brown in color.³³ Ectropion may develop if facial involvement is severe.^{33,36} A salmon-colored palmoplantar keratoderma with fissures is common and may be the presenting feature (Fig. 16.11D). Over time, the follicular component may be lost and psoriasiform morphology becomes more prominent, especially on the knees and elbows. Nails have longitudinal ridges and subungual hyperkeratosis but pitting and ‘oil spots’ characteristic of psoriasis are notably absent.³³ Pruritus, if present, is usually mild. Sweating may be impaired in affected skin.

Type IV circumscribed juvenile PRP is characterized by sharply demarcated areas of follicular hyperkeratosis that coalesce to form psoriasiform plaques on the elbows, knees, ankles, and dorsal aspects of the hands and feet. A waxy, orange-red, diffuse palmoplantar keratoderma may be observed. Scaly red patches may appear on other parts of the body and hyperkeratosis overlying bony prominences (elbows, knees, ankles, Achilles tendon) is common.^{33,40}

Type V atypical PRP is characterized by follicular hyperkeratosis, erythema and ichthyosiform dermatitis. The palms and soles may develop a sclerodermoid appearance with tethering and subsequent joint contractures (Fig. 16.13). The familial form of type V PRP exhibits autosomal dominant inheritance and presents at birth or in early infancy, often with head and neck involvement or diffuse erythroderma.^{37,38}

Acute, post-infectious PRP is morphologically similar to type III and occurs after the first year of life in the context of a recent infection. The initial presentation is abrupt, with rapidly progressing rash and systemic signs resembling superantigen-mediated diseases such as staphylococcal scalded skin syndrome (SSSS), scarlet fever, toxic shock syndrome or Kawasaki disease. The initial eruption is followed in days to weeks by the typical features of classic juvenile PRP.^{34,35,41}

Extracutaneous findings

There are no systemic abnormalities independently associated with PRP. Abnormalities identified in patients with post-infectious PRP are due to the underlying infection. Fluid imbalance and metabolic derangements may occur as a consequence of erythroderma.

Etiology and pathogenesis

The etiology and pathogenesis of PRP are not fully understood. PRP is primarily a sporadic disorder, with no clear sex or racial predilection. The observation of pediatric cases following bacterial or viral infections, vaccinations, and cutaneous trauma suggests a reactive process. Superantigens and massive cytokine release likely mediate the post-infectious cases.^{35,41,42} Familial cases point to disordered keratinization modulated by genetic predisposition. Recently, familial PRP, in four families with disease onset in the first 3 years of life, was found to result from mutations in CARD14. Interestingly, mutations of this gene have been identified in some cases of psoriasis, suggesting that inherited PRP and some forms of psoriasis are allelic.⁴³



Figure 16.12 Classic juvenile PRP. (A) Keratotic papules on the dorsal hands. (B) Waxy keratoderma of the soles.



Figure 16.11 (A,B) A 2 year-old child with classic juvenile PRP. Note the facial tightness and erythroderma admixed with islands of sparing. (C) Characteristic keratotic papules. (D) Waxy keratoderma.

The histopathologic features of PRP are found most often in erythrodermic areas and less so in areas of follicular hyperkeratosis. There is epidermal acanthosis with alternating orthokeratosis and parakeratosis in both vertical and horizontal directions. Perifollicular parakeratosis surrounds dilated, plugged hair follicles. A superficial dermal perivascular and perifollicular lymphocytic infiltrate is observed.⁴⁴

Differential diagnosis

The diagnosis most difficult to differentiate from PRP – both clinically and histopathologically – is psoriasis. The precise relationship between these diseases is unclear, and discriminating between the two in young infants may not be possible. Features favoring PRP include follicular keratotic papules, diffuse palmoplantar keratoderma, lack of mounds of neutrophils on histopathology, and the quality of scalp scale, which tends to be flaky white and powdery in PRP and thick and adherent in psoriasis.

The acute post-infectious form of PRP may be difficult to initially differentiate from superantigen-mediated diseases including SSSS, scarlet fever, Kawasaki disease, and toxic shock syndromes. Other entities in the differential diagnosis include follicular eczema, cutaneous drug eruptions, congenital ichthyosis, lichen planus and other lichenoid diseases, and keratosis pilaris. The circumscribed form may closely resemble progressive symmetric erythrodermatitis (PSEK), which is characterized by well-defined red scaly plaques symmetrically distributed on the face, extremities, and buttocks. Half of

patients with PSEK have palmoplantar keratoderma but follicular hyperkeratosis is not observed.

Prognosis

The course and prognosis of neonates and infants with PRP is unpredictable. The disease morphology and extent may evolve over time with or without treatment. Features that overlap with other forms of PRP or other diseases, such as psoriasis, may develop. In pediatric patients in general, outcomes do not correlate with acuity or severity. Acute erythrodermic and post-infectious PRP carry the most optimistic prognosis. These cases typically resolve without complication but resolution may be delayed for months despite treatment, and the disease may recur.^{45,46} The prognosis of circumscribed PRP is unclear, but it does not tend to progress or transition into other forms. Atypical juvenile PRP, including familial cases, runs a chronic course with little or no tendency to remit.³³

Treatment

Topical therapy is preferable in neonates and infants though responses are inconsistent. Topical anti-inflammatory options ideally delivered in oil or ointment vehicles include corticosteroids, calcineurin inhibitors, vitamin D analogs, and tar derivatives (LCD). Keratolytics such as urea and alpha-hydroxy acid may be helpful for thick scale. Topical retinoids may work but can irritate the skin. Topical salicylic acid should be avoided in infants because of the risk of salicylism. Bland emollients serve as adjunctive therapy to maintain the barrier.

In cases of extensive erythroderma, supportive care including attention to fluid and electrolyte balance and monitoring for cutaneous infection is a fundamental aspect of management. In addition to topical therapies, systemic medications may be warranted in severe, rapidly progressive or chronic and refractory cases. Oral retinoids (isotretinoin, acitretin) have the best outcome data in children and may clear the disease in weeks to months.^{35,36,47} Other systemic choices include oral vitamin A, cyclosporine⁴⁸ and methotrexate. Pruritus can be managed with oral antihistamines and secondary infection with oral antibiotics as indicated.

Narrow-band UVB phototherapy is variably effective but can be risky as some cases are exacerbated by ultraviolet light.⁴⁹ Phototherapy has been used successfully for PRP in children but there are no reports of its use in neonates or infants.

PITYRIASIS ROSEA

Introduction

Pityriasis rosea (PR) is a self-limited papulosquamous eruption, which has been reported in infants as young as 3 months of age.^{50–52} Less than 30 well-documented cases are reported in very young infants. Disease in this age group often presents atypically and is therefore likely to be misdiagnosed.^{51,53,54} A separate issue is pityriasis rosea in pregnant women; these cases may be associated with fetal infection with HHV-6, premature delivery, and fetal demise. The greatest fetal risk seems to be within the first 15 weeks' gestation. Pregnant women who develop pityriasis rosea should be referred for high-risk obstetrics evaluation.⁵⁵

Cutaneous findings

Classically, but not invariably, the onset of the disease is 'heralded' by a single round or ovoid flesh-colored or pink scaly



Figure 16.13 Type V PRP. (A) Early facial involvement in infancy. (B) Follicular hyperkeratosis, erythema and ichthyosiform dermatitis (on acitretin). (C) Waxy, salmon-colored palmar keratoderma and tapered 'sclerodermoid' fingers. (D) Waxy, fissured plantar keratoderma.

patch of variable size (Fig. 16.14A). The patch may appear anywhere on the body and exhibit central clearing with a raised border. The herald patch is followed in days to weeks by an eruption of smaller, variably sized, macules, papules and scaly patches (Fig. 16.14B). Four main distributions have been described in children: central (face and trunk), peripheral (arms and legs), inverse (axillary and inguinal) and diffuse.⁵⁶ Lesions on the trunk arise within Langer's skin cleavage lines and impart the appearance of a 'Christmas tree' pattern.⁵⁷ Individual patches are often annular with a pink to tan center of fine scales and a peripheral collarette of inward pointing scale. Oral lesions may be present. The eruption evolves for several weeks and occasionally several months before spontaneously healing. The disease recurs in approximately 2% of patients.^{52,58}

The full spectrum of cutaneous presentations in infants is as-yet unknown. A papular variant appears to be most common in infants. Other atypical morphologies include micropapular and vesicular. Unusual distributions comprise facial, inverse,

localized, unilateral, or acral involvement. Infants, toddlers, and black patients are more likely to have unconventional presentations (Fig. 16.15). Post-inflammatory pigment alteration may be observed for weeks to months after resolution of the eruption.^{54,59,60} Infants affected with PR may have signs of an upper respiratory or other viral illness such as irritability, poor feeding, low-grade fever and lymphadenopathy preceding or during the eruption.

Etiology and pathogenesis

Pityriasis rosea occurs worldwide without racial or sex predilection. The cause of PR remains unknown. Clinically and epidemiologically, PR best resembles an infectious disease. PR occurs throughout the year, but seasonal clustering of cases in cooler months and among social contacts together with rarity of recurrence supports an infectious etiology.^{58,59,61,62} Several infectious agents have been suggested; recently the role of human herpes virus (HHV)-6 and HHV-7 is being explored.⁶³



Figure 16.15 (A,B) Inverse pityriasis rosea in a young female child. (C) PR in a darker skinned child. Note herald patch on right lower flank.

Diagnosis of PR is based on history and clinical examination. A skin biopsy may rarely be needed to rule out alternative diagnoses. The histopathology of PR can be suggestive but not entirely specific. Most often, a superficial perivascular dermatitis comprised of slight epidermal hyperplasia, focal spongiosis, and focal parakeratosis in mounds is seen. Papillary dermal edema and a superficial perivascular infiltrate of lymphocytes, histiocytes and occasional eosinophils may be observed. Dyskeratotic keratinocytes in the epidermis and extravasated erythrocytes in the dermis are additional helpful clues in atypical cases.⁵³

Differential diagnosis, prognosis, and treatment

The herald patch of pityriasis rosea may be mistaken for tinea corporis, nummular dermatitis, psoriasis, neonatal lupus, or pityriasis alba. In infants, the eruption of PR must be distinguished from guttate psoriasis, nummular eczema, impetigo, secondary syphilis, neonatal lupus, urticaria, lichen planus, annular capillaritis, seborrheic dermatitis, tinea corporis, and erythema annulare centrifugum. Vesicular PR may be confused with varicella and other vesicular eruptions.

Pityriasis rosea is a self-limited disorder that typically resolves without complication in 6–8 weeks. Some cases may last several months. Treatment is primarily symptomatic, and therapy in infants is rarely necessary. Topical emollients, topical

corticosteroids, systemic antihistamines, and natural sunlight may be used for symptom control. Oral erythromycin has shown benefit in children as young as 1 year, but benefit of the drug versus spontaneous remission of the disease is questionable.⁶⁴

Lichenoid disorders

PITYRIASIS LICHENOIDES

Pityriasis lichenoides (PL) refers to a spectrum of conditions that, to date, defies straightforward classification. It is perhaps best regarded as a reactive inflammatory disorder, but evidence of T-cell clonality and rare progression to cutaneous lymphoma support the possibility that PL represents a lymphoproliferative process. These two etiologic viewpoints are not mutually exclusive. PL is classically divided into acute and chronic forms based on both clinical and histopathological features. In practice, clinical overlap between the two forms often exists. Both pityriasis lichenoides et varioliformis acuta (PLEVA, or Mucha–Habermann disease) and pityriasis lichenoides chronica (PLC) are rare in infants and exceedingly rare in newborns, with fewer than 10 cases reported in the first year of life.^{65–68} The incidence is higher in toddlers, school-aged children, and young adults.^{69,70}

The primary features of PLEVA and PLC are summarized in Table 16.4.

Cutaneous findings

PLEVA presents with recurrent crops of erythematous papules and papulovesicles that may be distributed on the trunk and proximal extremities, limited to just the distal extremities, or diffusely over the body (Fig. 16.16). Individual primary lesions evolve to develop central necrosis with hemorrhagic crusting and then gradually resolve over weeks, sometimes leaving post-inflammatory pigment alteration or varioliform scarring. Lesions in various stages of evolution may be seen simultaneously on a given patient.⁷⁰

A severe and potentially life-threatening variant of PLEVA, sometimes called ‘febrile ulceronecrotic Mucha–Habermann disease’ or ‘PLEVA fulminans’, has rarely been reported in infants.⁷¹ A widespread eruption of crusted and necrotic papules develops over days, with progression to hemorrhagic bullae and large, painful ulcers. Oral and genital mucosal ulcers may also be seen.

PLC is characterized by recurrent crops of skin-colored, pink, red, or red-brown scaly papules distributed over the trunk and extremities. As individual lesions evolve, they may flatten and become less scaly, ultimately involuting over a period of



Figure 16.14 Pityriasis rosea in two young children. (A) Herald patch on left chest. (B) Papulosquamous eruption following Langer's lines.

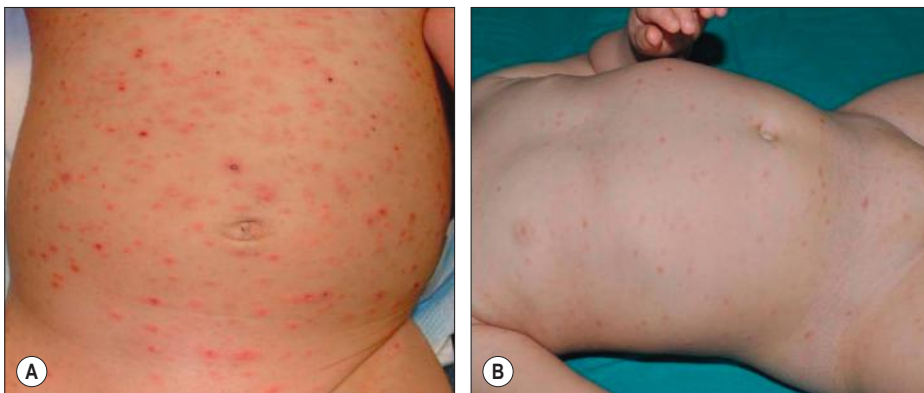


Figure 16.16 Pityriasis lichenoides (PLEVA). (A) A 16-month-old child. (B) A 9-month-old child. (Courtesy of Dr Angela Hernandez-Martin.)

TABLE
16.4

Major features of PLEVA and PLC

	PLEVA	PLC
Primary morphology	Erythematous papules with hemorrhagic crusting or central necrosis	Red-brown scaly papules and hypopigmented macules
Lesion duration	Weeks	Weeks to months
Residual findings	Varioliform scarring or pigment alteration	Hypopigmentation
Histologic features	Dense lymphocytic infiltrate, keratinocyte necrosis, extravasated erythrocytes	Sparse lymphocytic infiltrate, rare keratinocyte necrosis, minimal extravasated erythrocytes
Disease duration	Months to years	Months to years

PLEVA, pityriasis lichenoides et varioliformis acuta; PLC, pityriasis lichenoides chronica.

weeks to months. Hypopigmented macules or patches are also commonly seen, both in areas of previous papules, where they likely represent post-inflammatory hypopigmentation, and at times in areas without apparent prior inflammatory papules (Fig. 16.17). Rarely, hypopigmented macules may be the primary presenting morphology in the absence of papules.⁶⁵ In contrast to PLEVA, hemorrhagic crusting and necrosis are not observed in pure PLC; however, overlapping morphologies of PLC and PLEVA are common. Both PLEVA and PLC may be asymptomatic or pruritic.

Extracutaneous findings

The findings of PL are typically limited to the skin, though low-grade fever or malaise may occur. In PLEVA fulminans, high fever is characteristic and may be accompanied by bacterial superinfection leading to sepsis, oral aversion and dehydration secondary to mucosal ulceration, and laryngeal edema requiring endotracheal intubation.⁷¹

Etiology and pathogenesis

The pathogenesis of PL is poorly understood. A reaction to a foreign antigen or set of antigens may trigger infiltration of T

lymphocytes into lesional skin. Candidate antigens include viral particles and other infectious agents, though symptoms of a prodromal illness are elicited only in a minority of patients. Implicated triggers have included parvovirus B19, human herpesvirus 8, *Streptococcus* species, and measles-mumps-rubella vaccine.^{65,70,72,73} In most cases, no specific trigger can be identified.

The histopathologic findings of PL include a superficial perivascular and lichenoid lymphocytic infiltrate with vacuolar alteration of the basal layer. In PLEVA, there is parakeratosis, individual necrotic keratinocytes in the epidermis, and extravasation of erythrocytes in the papillary dermis. The findings in PLC are similar but more subtle, with a sparser infiltrate, fewer necrotic keratinocytes, and a lesser degree of erythrocyte extravasation. Cytotoxic CD8+ T lymphocytes are more numerous in PLEVA, while CD4+ lymphocytes and regulatory T cells are found in greater numbers in PLC.⁷²

Some cases of PL are found to contain clonal populations of T-cells. Whether this finding suggests that PL is a primary lymphoproliferative disease with malignant potential, or instead is a reactive process with secondary clonal expansion, is a matter of continued controversy. To date, only one case of PL in an infant progressing to cutaneous lymphoma has been reported, and in that case, the time between disease onset and malignant progression was greater than 10 years.⁷⁴

Differential diagnosis

The eruptive crops of crusted papules and papulovesicles of PLEVA may resemble varicella, scabies or other arthropod assaults, drug eruptions, cutaneous small-vessel vasculitis, and Langerhans' cell histiocytosis. PLEVA fulminans may resemble disseminated herpes simplex infection, meningococcemia, or Stevens–Johnson syndrome. The scaly papules and hypopigmented macules of PLC may resemble guttate psoriasis, pityriasis rosea, lichen planus, or hypopigmented mycosis fungoides. Both PLEVA and PLC may be confused with lymphomatoid papulosis, which is distinguished from PL by a smaller number of larger papulonodules, which, on biopsy, reveal large, atypical CD30+ lymphocytes.

Prognosis and treatment

The course of PL is variable, and multiple relapses are common prior to eventual disease resolution. The individual lesions of PLEVA tend to resolve spontaneously in weeks, while those of PLC resolve somewhat slower, in weeks to months. It may take anywhere from a few months to more than 10 years for PL to fully resolve.⁶⁵

As the disease is self-resolving, treatment is not usually required; however, some cases of PLEVA do leave scars. Symptoms of pruritus or skin irritation can be managed with emollients, topical corticosteroids, and oral antihistamines. Oral erythromycin, administered for at least 3 months, may be effective at decreasing the duration of disease in some patients.⁷⁵ Oral tetracyclines are not an option in infants due to dental side-effects. Phototherapy, though technically challenging with a young infant, may also be helpful for PL; a trial of cautious natural sunlight exposure is a cost-effective alternative.

For PLEVA fulminans, treatment is critical, as this condition may be fatal. A report of two infants with PLEVA fulminans has demonstrated the effectiveness of methotrexate combined with systemic corticosteroids for treating this condition.⁷¹



Figure 16.17 Pityriasis lichenoides. (A) A 3-year-old child with pink papules admixed with hypopigmented macules. (B) A young child with relatively milder disease on his sun-exposed arm compared with his sun-protected leg. Incidental melanocytic nevi are noted.

LICHEN PLANUS

Lichen planus is the prototypical lichenoid eruption, characterized by flat-topped, violaceous papules. It is primarily a disease of adults, with 10% or fewer of all cases occurring in children.⁷⁶ Of these, only a small fraction occurs in infants: in one report of 87 cases of juvenile lichen planus, only nine patients were under age 2.⁷⁷ Onset prior to age 5 months has not been reported.^{78,79}

Cutaneous findings

The hallmark primary lesion of lichen planus is a pruritic, violaceous, shiny, flat-topped papule. The papules tend to be several millimeters in diameter and polygonal in shape, though they may coalesce into larger, more irregularly-shaped plaques (Fig. 16.18A–C). A fine, whitish, lacy network, known as Wickham's striae, may be visible on the surface of some lesions and can aid diagnosis (Fig. 16.18D). Almost all cases of lichen planus reported in infants have been of a linear variant, usually along an extremity.^{77,78,80,81} Nail dystrophy and reticulate plaques of the oral mucosa have not been reported in infants, though these changes are sometimes observed in older children and often seen in adults. In children, sites of predilection include the extremities, especially on the flexor aspects, and the lower back.^{77,79,80} Because lichen planus exhibits the Koebner phenomenon (occurrence in sites of trauma), the knees and elbows may be involved in children who crawl or play on the ground. No extracutaneous findings have been reported in neonates or infants.

Etiology and pathogenesis

The pathogenesis of lichen planus is unknown, though it appears to involve a T-cell mediated reaction to an antigenic trigger in a susceptible host. Several cases of lichen planus in older children arising after hepatitis B vaccine have been reported, and in adults, lichen planus is sometimes associated with underlying viral hepatitis, suggesting that exposure to a viral particle may trigger the reactive process.⁸²

The histology of lichen planus reveals a dense, band-like lymphocytic infiltrate obscuring the dermal–epidermal junction. There is compact orthokeratosis of the stratum corneum, hypergranulosis, and 'saw-toothing' of the rete with vacuolar

alteration of the basal layer. Single necrotic keratinocytes may be seen in the epidermis or in the superficial papillary dermis.

Differential diagnosis, prognosis, and treatment

The flat-topped papules of lichen planus may resemble psoriasis, pityriasis lichenoides, and flat warts. In infants with linear lichen planus, lichen striatus is the primary entity on the differential diagnosis. Compared with linear lichen planus, lichen striatus tends to arise 'fully formed' over a shorter period of time, more commonly follows Blaschko's lines, and is less often pruritic. Linear psoriasis, linear porokeratosis, and epidermal nevi should also be considered in the differential diagnosis.

Lichen planus follows a subacute to chronic course, which may resolve spontaneously over a period of months to years; post-inflammatory pigment alteration is common. Resolution can be hastened, and pruritus minimized, with mid- to high-potency topical corticosteroids. Treatment for several months is often required. Systemic corticosteroids can be considered in severe disease. Oral antihistamines may be useful for controlling pruritus. Phototherapy or natural sunlight exposure may be helpful in some patients but may aggravate disease in others, so caution should be exercised.

LICHEN STRIATUS

Unlike lichen planus, lichen striatus is primarily a childhood disorder, with most cases occurring in pre school-age children.⁸³ Numerous cases in infants have been reported.^{84,85}

Cutaneous findings

Lichen striatus tends to develop rather acutely, over a period of days to weeks, with erythematous, tan, or skin colored papules erupting in a linear or whorled arrangement along the lines of Blaschko. The individual constituent papules may be shiny and flat-topped or may be scaly. Early in its development, lichen striatus may appear inflamed and be somewhat pruritic, but fully developed lesions tend to be bland, flesh-colored to hypopigmented, and most often asymptomatic (Fig. 16.19). As lichen striatus evolves, it often leaves behind post-inflammatory pigment alteration, most commonly hypopigmentation. Nail



Figure 16.18 Lichen planus. (C) Classic findings of LP in an older child. (D) Wickham's striae are visible on the surface of the lesions.

Figure 16.18 Lichen planus. (A) A 4-year-old child with characteristic purple polygonal papules on the flexor wrist. (B) Discrete and coalescent papular and annular lesions on the knees.

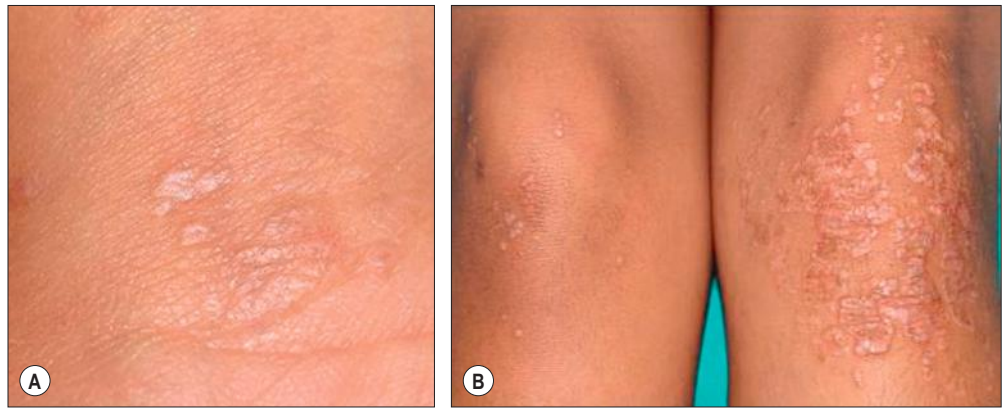
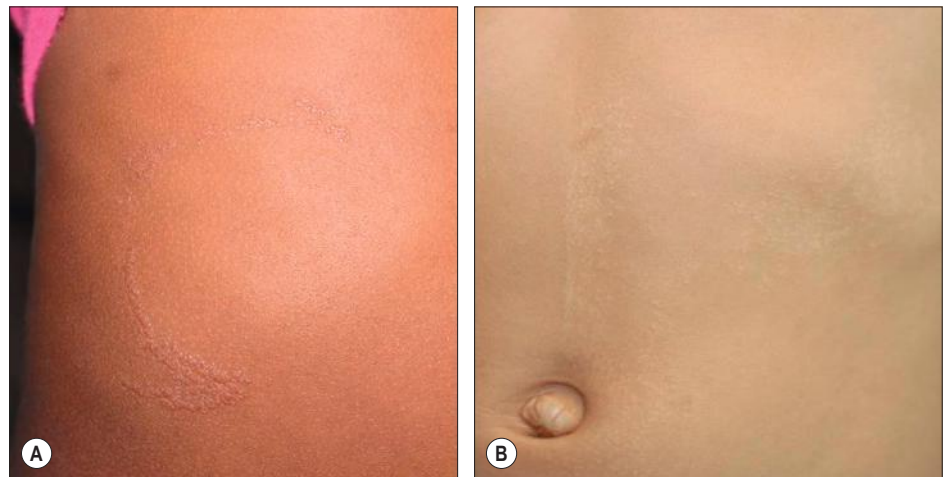


Figure 16.19 Lichen striatus. (A) Acute, inflamed lichen striatus following the lines of Blaschko. (B) Chronic lichen striatus appearing predominantly hypopigmented.



dystrophy, with linear longitudinal ridging and splitting of the nail plate, may be seen when lichen striatus involves a digit⁸⁶ (Fig. 16.20). No extracutaneous findings have been reported.

Etiology and pathogenesis

The pathogenesis of lichen striatus is unknown, but a cytotoxic T-cell mediated reaction to a virus or other foreign antigen has been suspected. Support for a viral etiology comes from the higher incidence of disease in young children compared with adults, the occasional co-occurrence in siblings, and the tendency for seasonal clustering of cases. Lichen striatus is seen more commonly in the autumn and winter months of the northern hemisphere and the spring and summer months of the southern hemisphere.^{85,87} Occurrence in an infant following BCG vaccination has been reported.⁸⁸

The Blaschkoid distribution suggests that only a subpopulation of keratinocytes, presumably all derived from a single embryonic precursor, are susceptible to the inflammatory reaction. These keratinocytes may display an aberrant epitope that cross-reacts with the primary triggering antigen.

The histology of lichen striatus is notable for a band-like lymphocytic infiltrate along the dermal–epidermal junction, with extension of the infiltrate down adnexal structures. Focal parakeratosis, spongiosis, and isolated necrotic keratinocytes may be seen.

Differential diagnosis

Lichen striatus should be distinguished from linear lichen planus, which tends to be more gradual in onset and more pruritic. Lichen striatus is also more likely to resolve with residual hypopigmentation, whereas linear lichen planus is more likely to resolve with hyperpigmentation. The

differential diagnosis also includes epidermal nevus, particularly inflammatory linear verrucous epidermal nevus (ILVEN). ILVEN is usually more pruritic than lichen striatus and does not resolve spontaneously. Other entities to consider include linear psoriasis and linear porokeratosis. Incontinentia pigmenti also follows Blaschko's lines, but typically presents in the newborn period and is usually more vesicular or verrucous.

Prognosis and treatment

Lichen striatus resolves spontaneously without intervention. The average duration is approximately 6–12 months, but some cases last considerably longer and residual hypopigmentation may persist for several years.^{83,87} Topical corticosteroids and emollients may be applied for pruritus, but they do not decrease the duration of disease or affect the degree of postinflammatory pigment alteration.

LICHEN NITIDUS

Lichen nitidus is a distinctive inflammatory disorder that tends to affect children and young adults, but can affect infants. It has not yet been described in newborns.

Cutaneous findings

The primary lesion of lichen nitidus is a pinpoint, skin-colored papule with a shiny, flat-topped surface (Fig. 16.21A–D). Monomorphic papules usually occur in clusters, most frequently on the upper trunk, volar wrists, dorsal hands, and the genitalia. The central face may also be involved. A generalized variant has been described in infants.^{89,90} Pruritus may accompany the generalized form and sometimes the localized form, but typically the lesions are asymptomatic. Koebnerization is common. A rare photo-distributed form, called 'lichen nitidus actinicus', has not been reported in infants to date. Several case reports have described lichen nitidus occurring in infants with Down syndrome.^{90,91} Juvenile arthritis arising several months after the onset of lichen nitidus in an infant has also been described, but that association may have been coincidental.⁸⁹

Etiology and pathogenesis

The pathogenesis of lichen nitidus is unknown. In most cases, no inciting trigger can be identified, but several reports in older children of photodistributed lichen nitidus (lichen nitidus actinicus) suggest that sun exposure may sometimes be contributory;⁸⁰ this may reflect a Koebner phenomenon.

The histologic features of lichen nitidus are highly distinctive. A granulomatous collection of histiocytes and lymphocytes is seen in the papillary dermis, which is flanked on either side by elongated rete ridges, giving the appearance of a 'ball in claw.' There may be overlying parakeratosis and thinning of the epidermis with vacuolar alteration of the basal layer.

Differential diagnosis, prognosis, and treatment

The minute papules of lichen nitidus may resemble lichen spinulosus or keratosis pilaris, though those conditions are characterized by folliculocentric papules that usually have a central keratotic spine. Papular eczema may resemble generalized lichen nitidus, but the papules of lichen nitidus tend to be more discrete. Other entities on the differential diagnosis include micropapular lichen planus, flat warts, and an id reaction.



Figure 16.20 (A,B) Lichen striatus in a 2-year-old child extending from the upper arm to fingertip, resulting in nail dystrophy.

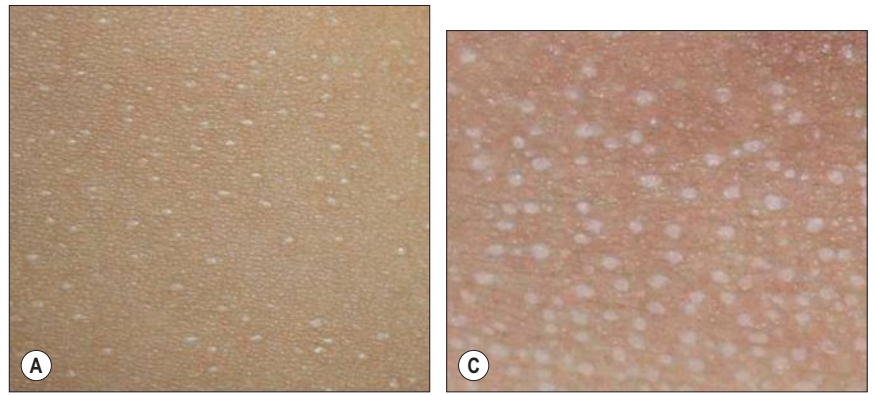


Figure 16.21 Lichen nitidus. (A) Individual pinpoint flat-topped flesh-colored papules in a child with generalized lichen nitidus. (C) Close-up of primary lesions.



Figure 16.21 Lichen nitidus. (B) Linear Koebner reaction due to scratching. (D) Clustered on the dorsal hand.

Lichen nitidus tends to resolve spontaneously over years. Treatment is rarely indicated, though in patients with pruritus, topical corticosteroids, emollients, oral antihistamines, and phototherapy may be of benefit.

KERATOSIS LICHENOIDES CHRONICA

Keratosis lichenoides chronica (KLC) is a rare, chronic disorder with histologic features similar to lichen planus but with unique morphologic characteristics. Some early reports of lichen planus in infants may, in retrospect, have described what would now be considered KLC.^{92,93}

KLC has recently been delineated into juvenile and adult forms.⁹⁴ The juvenile form, which often begins in the newborn period or within the first year of life, tends to show sparing of the nails and mucosal surfaces, alopecia of the upper face, and occasional involvement of sibling pairs. By contrast, in the adult form, the nails and mucosa are often involved, alopecia is not associated, and the disease tends to occur in a sporadic fashion.

Cutaneous findings

In infants, lesions of KLC tend to appear first on the face.⁹⁴ Facial lesions favor the cheeks, chin, and ears, where a variety of morphologies may be seen: well-demarcated erythematous plaques with seborrhea-like scale, polycyclic erythematous plaques with an accentuated border, or purpuric patches, all of which may evolve to leave hyperpigmentation.^{94–96} Alopecia of the eyebrows, eyelashes, and forehead may be observed.⁹⁴ On the extensor extremities and buttocks, hyperkeratotic, erythematous to violaceous papules develop, which coalesce to form

linear or reticulated plaques. The lesions of KLC may be pruritic but are often asymptomatic. No extracutaneous findings have been reported in infants.

Etiology and pathogenesis

The pathogenesis of KLC is unknown. The histologic features of KLC resemble those seen in lichen planus, with a dense band-like lymphocytic infiltrate along the dermal–epidermal junction, vacuolar alteration of the basal layer, irregular acanthosis of the epidermis, hyperkeratosis, and focal parakeratosis.

Differential diagnosis, prognosis, and treatment

The facial lesions of KLC may resemble seborrheic dermatitis or lupus erythematosus. Lichen planus may also present with hyperkeratotic papules and plaques on the extremities, but the linear configuration and resistance to treatment of KLC are relatively specific features.

KLC is a progressive disorder that evolves over years to decades. Phototherapy may produce modest improvements, but no treatments have consistently shown efficacy in controlling this condition.⁹⁷ Systemic retinoids are a therapeutic option in older children with severe disease but have not been reported in infants.

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Figures 4, 5, 7, 12, 15, 18A, B, 19 and 21A, C are available online at [ExpertConsult.com](https://www.expertconsult.com)

Tables 2, 3 and 4, are available online at [ExpertConsult.com](https://www.expertconsult.com)

KEY REFERENCES

4. Morris A, Rogers M, Fischer G, et al. Childhood psoriasis: a clinical review of 1262 cases. *Pediatr Dermatol* 2001;18(3):188–98.
5. Bhutani T, Kamangar F, Cordoro KM. Management of pediatric psoriasis. *Pediatr Ann* 2012; 41(1):e1–7.
30. Cordoro KM. Management of childhood psoriasis. *Adv Dermatol* 2008;24:125–69.
34. Larregue M, Champion R, Bressieux JM, et al. Acute pityriasis rubra pilaris in the child. Apropos of 4 cases. *Ann Dermatol Venerol* 1983;110(3):221–8.
36. Allison DS, El-Azhary RA, Calobrisi SD, et al. Pityriasis rubra pilaris in children. *J Am Acad Dermatol* 2002;47(3):386–9.
56. Gunduz O, Ersoy-Evans S, Karaduman A. Childhood pityriasis rosea. *Pediatr Dermatol* 2009; 26(6):750–1.
65. Ersoy-Evans S, Greco MF, Mancini AJ, et al. Pityriasis lichenoides in childhood: a retrospective review of 124 patients. *J Am Acad Dermatol* 2007;56(2):205–10.
71. Kaufman WS, McNamara EK, Curtis AR, et al. Febrile ulceronecrotic Mucha-Habermann disease (pityriasis lichenoides et varioliformis acuta fulminans) presenting as Stevens-Johnson syndrome. *Pediatr Dermatol* 2012;29(2):135–40.
85. Kennedy D, Rogers M. Lichen striatus. *Pediatr Dermatol* 1996;13(2):95–9.
94. Ruiz-Maldonado R, Duran-McKinster C, Orozco-Covarrubias L, et al. Keratosis lichenoides chronica in pediatric patients: a different disease? *J Am Acad Dermatol* 2007;56(2 Suppl): S1–5.

REFERENCES

- Tollefson MM, Crowson CS, McEvoy MT, et al. Incidence of psoriasis in children: a population-based study. *J Am Acad Dermatol* 2010;62(6):979–87.
- Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. *Dermatologica* 1974;148(1):1–18.
- Burden AD. Management of psoriasis in childhood. *Clin Exp Dermatol* 1999;24(5):341–5.
- Morris A, Rogers M, Fischer G, et al. Childhood psoriasis: a clinical review of 1262 cases. *Pediatr Dermatol* 2001;18(3):188–98.
- Bhutani T, Kamangar F, Cordero KM. Management of pediatric psoriasis. *Pediatr Ann* 2012;41(1):e1–7.
- Benoit S, Hamm H. Childhood psoriasis. *Clin Dermatol* 2007;25(6):555–62.
- Menni S, Gualandri L, Boccardi D, et al. Association of psoriasis-like eruption and Kawasaki disease. *J Dermatol* 2006;33(8):571–3.
- Rattet JP, Headley JL, Barr RJ. Diaper dermatitis with psoriasiform ID eruption. *Int J Dermatol* 1981;20(2):122–5.
- Neville EA, Finn OA. Psoriasiform napkin dermatitis—a follow-up study. *Br J Dermatol* 1975;92(3):279–85.
- Boje Rasmussen H, Hagdrup H, Schmidt H. Psoriasiform napkin dermatitis. *Acta Derm Venereol* 1986;66(6):534–6.
- Farber EM, Mullen RH, Jacobs AH, et al. Infantile psoriasis: a follow-up study. *Pediatr Dermatol* 1986;3(3):237–43.
- Salleras M, Sanchez-Regana M, Umberto P. Congenital erythrodermic psoriasis: case report and literature review. *Pediatr Dermatol* 1995;12(3):231–4.
- Pruszkowski A, Bodemer C, Fraïtag S, et al. Neonatal and infantile erythrodermas: a retrospective study of 51 patients. *Arch Dermatol* 2000;136(7):875–80.
- Frost P, Van Scott EJ. Ichthyosiform dermatoses. Classification based on anatomic and biometric observations. *Arch Dermatol* 1966;94(2):113–26.
- Bellet JS, Chamlin SL, Yan AC, et al. Intertriginous pustular psoriasis. *J Am Acad Dermatol* 2009;60(4):679–83.
- Aksentijevich I, Masters SL, Ferguson PJ, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *N Engl J Med* 2009;360(23):2426–37.
- Minkis K, Aksentijevich I, Goldbach-Mansky R, et al. Interleukin 1 receptor antagonist deficiency presenting as infantile pustulosis mimicking infantile pustular psoriasis. *Arch Dermatol* 2012;148(6):747–52.
- Pereira TM, Vieira AP, Fernandes JC, et al. Anti-TNF-alpha therapy in childhood pustular psoriasis. *Dermatology* 2006;213(4):350–2.
- Lehman JS, Rahil AK. Congenital psoriasis: case report and literature review. *Pediatr Dermatol* 2008;25(3):332–8.
- Lehners-Weber C, de la Brassinne M, Dezfoulian B, et al. Congenital psoriasis following the lines of Blaschko. *Pediatr Dermatol* 1996;13(3):219–21.
- Shwayder T, Banerjee S. Netherton syndrome presenting as congenital psoriasis. *Pediatr Dermatol* 1997;14(6):473–6.
- Atherton DJ, Kahana M, Russell-Jones R. Naevoid psoriasis. *Br J Dermatol* 1989;120(6):837–41.
- Stoll ML, Lio P, Sundel RP, et al. Comparison of Vancouver and International League of Associations for rheumatology classification criteria for juvenile psoriatic arthritis. *Arthritis Rheum* 2008;59(1):51–8.
- Paller AS, Mercy K, Kwasny MJ, et al. Association of Pediatric Psoriasis Severity with excess and central adiposity: an international cross-sectional study. *Arch Dermatol* 2012;19:1–11.
- Au SC, Goldminz AM, Loo DS, et al. Association between pediatric psoriasis and the metabolic syndrome. *J Am Acad Dermatol* 2012;66(6):1012–13.
- Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009;361(5):496–509.
- Zvulunov A, Greenberg D, Cagnano E, et al. Development of psoriatic lesions during acute and convalescent phases of Kawasaki disease. *J Paediatr Child Health* 2003;39(3):229–31.
- Yoon S, Oh ST, Lee JY, et al. Plaque type psoriasiform eruption following Kawasaki disease. *Pediatr Dermatol* 2007;24(3):336–7.
- Tiilikainen A, Lassus A, Karvonen J, et al. Psoriasis and HLA-Cw6. *Br J Dermatol* 1980;102(2):179–84.
- Cordero KM. Management of childhood psoriasis. *Adv Dermatol* 2008;24:125–69.
- Mercy K, Kwasny M, Cordero KM, et al. Clinical manifestations of pediatric psoriasis: results of a multicenter study in the United States. *Pediatr Dermatol* 2013;30(4):424–8.
- Griffiths WA. Pityriasis rubra pilaris – an historical approach. 2. Clinical features. *Clin Exp Dermatol* 1976;1(1):37–50.
- Griffiths WA. Pityriasis rubra pilaris. *Clin Exp Dermatol* 1980;5(1):105–12.
- Larregue M, Champion R, Bressieux JM, et al. Acute pityriasis rubra pilaris in the child. Apropos of 4 cases. *Ann Dermatol Venereol* 1983;110(3):221–8.
- Ferrandiz-Pulido C, Bartralot R, Bassas P, et al. Acute postinfectious pityriasis rubra pilaris: a superantigen-mediated dermatosis. *Actas Dermosifiliogr* 2009;100(8):706–9.
- Allison DS, El-Azhary RA, Calobrisi SD, et al. Pityriasis rubra pilaris in children. *J Am Acad Dermatol* 2002;47(3):386–9.
- Vanderhooft SL, Francis JS, Holbrook KA, et al. Familial pityriasis rubra pilaris. *Arch Dermatol* 1995;131(4):448–53.
- Thomson MA, Moss C. Pityriasis rubra pilaris in a mother and two daughters. *Br J Dermatol* 2007;157(1):202–4.
- Al-Dhalimi MA. Neonatal and infantile erythroderma: a clinical and follow-up study of 42 cases. *J Dermatol* 2007;34(5):302–7.
- Albert MR, Mackool BT. Pityriasis rubra pilaris. *Int J Dermatol* 1999;38(1):1–11.
- Betlloch I, Ramon R, Silvestre JF, et al. Acute juvenile pityriasis rubra pilaris: a superantigen mediated disease? *Pediatr Dermatol* 2001;18(5):411–14.
- Mohrenschlager M, Abeck D. Further clinical evidence for involvement of bacterial superantigens in juvenile pityriasis rubra pilaris (PRP): report of two new cases. *Pediatr Dermatol* 2002;19(6):569.
- Fuchs-Telem D, Sarig O, van Steensel MA, et al. Familial pityriasis rubra pilaris is caused by mutations in CARD14. *Am J Hum Genet* 2012;91(1):163–70.
- Soeprono FF. Histologic criteria for the diagnosis of pityriasis rubra pilaris. *Am J Dermatopathol* 1986;8(4):277–83.
- Davidson CL Jr, Winkelmann RK, Kierland RR. Pityriasis rubra pilaris. A follow-up study of 57 patients. *Arch Dermatol* 1969;100(2):175–8.
- Gelmetti C, Schiuma AA, Cerri D, et al. Pityriasis rubra pilaris in childhood: a long-term study of 29 cases. *Pediatr Dermatol* 1986;3(6):446–51.
- Yang CC, Shih IH, Lin WL, et al. Juvenile pityriasis rubra pilaris: report of 28 cases in Taiwan. *J Am Acad Dermatol* 2008;59(6):943–8.
- Wetzig T, Sticherling M. Juvenile pityriasis rubra pilaris: successful treatment with ciclosporin. *Br J Dermatol* 2003;149(1):202–3.
- Khoo L, Asawanonda P, Grevelink SA, et al. Narrow-band UVB-associated lesional blisters in pityriasis rubra pilaris. *J Am Acad Dermatol* 1999;41(5 Pt 1):803–4.
- Hyatt HW Sr. Pityriasis rosea in a three month old infant. *Arch Pediatr* 1960;77:364–8.
- Rudusky BM. Pityriasis rosea in a 4-month-old infant; an account of suggested contagiousness. *J Pediatr* 1963;62:159–60.
- Hendricks AA, Lohr JA. Pityriasis rosea in infancy. *Arch Dermatol* 1979;115(7):896–7.
- Repiso T, Gonzalez-Castro U, Luelmo J, et al. Atypical pityriasis rosea in a 2-year-old. *Pediatr Dermatol* 1995;12(1):63–5.
- Zawar V. Acral pityriasis rosea in an infant with palmoplantar lesions: A novel manifestation. *Indian Dermatol Online J* 2010;1(1):21–3.
- Drago F, Broccolo F, Zaccaria E, et al. Pregnancy outcome in patients with pityriasis rosea. *J Am Acad Dermatol* 2008;58(5 Suppl 1):S78–83.
- Gunduz O, Ersoy-Evans S, Karaduman A. Childhood pityriasis rosea. *Pediatr Dermatol* 2009;26(6):750–1.
- Chuh AA. Rash orientation in pityriasis rosea: a qualitative study. *Eur J Dermatol* 2002;12(3):253–6.
- Chuang TY, Ilstrup DM, Perry HO, et al. Pityriasis rosea in Rochester, Minnesota, 1969 to 1978. *J Am Acad Dermatol* 1982;7(1):80–9.
- Gonzalez LM, Allen R, Janniger CK, et al. Pityriasis rosea: an important papulosquamous disorder. *Int J Dermatol* 2005;44(9):757–64.
- Amer A, Fischer H, Li X. The natural history of pityriasis rosea in black American children: how correct is the 'classic' description? *Arch Pediatr Adolesc Med* 2007;161(5):503–6.
- Cohen EL. Pityriasis rosea. *Br J Dermatol* 1967;79(10):533–7.
- Rebora A, Drago F, Broccolo F. Pityriasis rosea and herpesviruses: facts and controversies. *Clin Dermatol* 2010;28(5):497–501.
- Watanabe T, Kawamura T, Eyes S, et al. Pityriasis rosea (PR) is associated with reactivation of both human herpesvirus (HHV) -7 and -6 in blood. *J Invest Dermatol* 2000;114:784.
- Chuh AA, Dofitas BL, Comisel GG, et al. Interventions for pityriasis rosea. *Cochrane Database Syst Rev* 2007;(2):CD005068.
- Ersoy-Evans S, Greco MF, Mancini AJ, et al. Pityriasis lichenoides in childhood: a retrospective review of 124 patients. *J Am Acad Dermatol* 2007;56(2):205–10.
- Hoshina D, Akiyama M, Hamasaka K, et al. An infantile case of pityriasis lichenoides et varioliformis acuta. *Br J Dermatol* 2007;157(1):194–6.

67. Chand S, Srivastava N, Khopkar U, et al. Pityriasis lichenoides chronica: onset at birth. *Pediatr Dermatol* 2008;25(1):135–6.
68. Lopez-Villaescusa MT, Hernandez-Martin A, Colmenero I, et al. Pityriasis lichenoides in a 9-month-old boy. *Actas Dermosifiliogr* 2012 Nov 20.
69. Wahie S, Hiscutt E, Natarajan S, et al. Pityriasis lichenoides: the differences between children and adults. *Br J Dermatol* 2007;157(5):941–5.
70. Fernandes NF, Rozdeba PJ, Schwartz RA, et al. Pityriasis lichenoides et varioliformis acuta: a disease spectrum. *Int J Dermatol* 2010;49(3):257–61.
71. Kaufman WS, McNamara EK, Curtis AR, et al. Febrile ulceronecrotic Mucha-Habermann disease (pityriasis lichenoides et varioliformis acuta fulminans) presenting as Stevens-Johnson syndrome. *Pediatr Dermatol* 2012;29(2):135–40.
72. Kim JE, Yun WJ, Mun SK, et al. Pityriasis lichenoides et varioliformis acuta and pityriasis lichenoides chronica: comparison of lesional T-cell subsets and investigation of viral associations. *J Cutan Pathol* 2011;38(8):649–56.
73. Gil-Bistes D, Kluger N, Bessis D, et al. Pityriasis lichenoides chronica after measles-mumps-rubella vaccination. *J Dermatol* 2012;39(5):492–3.
74. Niemczyk UM, Zollner TM, Wolter M, et al. The transformation of pityriasis lichenoides chronica into parakeratosis variegata in an 11-year-old girl. *Br J Dermatol* 1997;137(6):983–7.
75. Hapa A, Ersoy-Evans S, Karaduman A. Childhood pityriasis lichenoides and oral erythromycin. *Pediatr Dermatol* 2012;29(6):719–24.
76. Luis-Montoya P, Dominguez-Soto L, Vega-Memije E. Lichen planus in 24 children with review of the literature. *Pediatr Dermatol* 2005;22(4):295–8.
77. Handa S, Sahoo B. Childhood lichen planus: a study of 87 cases. *Int J Dermatol* 2002;41(7):423–7.
78. Kanwar AJ, Kaur S, Rajagopalan M, et al. Lichen planus in an 8-month-old. *Pediatr Dermatol* 1989;6(4):358–9.
79. Sharma R, Maheshwari V. Childhood lichen planus: a report of fifty cases. *Pediatr Dermatol* 1999;16(5):345–8.
80. Kanwar AJ, Kaur S. Lichen nitidus actinicus. *Pediatr Dermatol* 1991;8(1):94–5.
81. Dhar S, Dawn G, Kanwar AJ. Linear lichen planus in an infant. *Pediatr Dermatol* 1994;11(4):363.
82. Limas C, Limas CJ. Lichen planus in children: a possible complication of hepatitis B vaccines. *Pediatr Dermatol* 2002;19(3):204–9.
83. Peramiquel L, Baselga E, Dalmau J, et al. Lichen striatus: clinical and epidemiological review of 23 cases. *Eur J Pediatr* 2006;165(4):267–9.
84. Taieb A, el Youbi A, Grosshans E, et al. Lichen striatus: a Blaschko linear acquired inflammatory skin eruption. *J Am Acad Dermatol* 1991;25(4):637–42.
85. Kennedy D, Rogers M. Lichen striatus. *Pediatr Dermatol* 1996;13(2):95–9.
86. Markouch I, Clerici T, Saiag P, et al. Lichen striatus with nail dystrophy in an infant. *Ann Dermatol Venereol* 2009;136(12):883–6.
87. Patrizi A, Neri I, Fiorentini C, et al. Lichen striatus: clinical and laboratory features of 115 children. *Pediatr Dermatol* 2004;21(3):197–204.
88. Hwang SM, Ahn SK, Lee SH, et al. Lichen striatus following BCG vaccination. *Clin Exp Dermatol* 1996;21(5):393–4.
89. Bercedo A, Cabero MJ, Garcia-Consuegra J, et al. Generalized lichen nitidus and juvenile chronic arthritis: an undescribed association. *Pediatr Dermatol* 1999;16(5):406–7.
90. Laxmisha C, Thappa DM. Generalized lichen nitidus with Down syndrome. *J Eur Acad Dermatol Venereol* 2006;20(9):1156–7.
91. Henry M, Metry DW. Generalized lichen nitidus, with perioral and perinasal accentuation, in association with Down syndrome. *Pediatr Dermatol* 2009;26(1):109–11.
92. Davies JH. Lichen Planus in an Infant. *Proc R Soc Med* 1934;28(2):112–13.
93. Anderson TE. Lichen planus in an infant. *Br J Dermatol* 1952;64(2):68–9.
94. Ruiz-Maldonado R, Duran-McKinster C, Orozco-Covarrubias L, et al. Keratosis lichenoides chronica in pediatric patients: a different disease? *J Am Acad Dermatol* 2007;56(2 Suppl):S1–5.
95. Torrelo A, Mediero IG, Zambrano A. Keratosis lichenoides chronica in a child. *Pediatr Dermatol* 1994;11(1):46–8.
96. Redondo P, Solano T. Keratosis lichenoides chronica in childhood. *Clin Exp Dermatol* 2002;27(4):283–5.
97. Tomb R, Soutou B. Keratosis lichenoides chronica in two siblings with marked response to UVB phototherapy. *Ann Dermatol Venereol* 2008;135(12):835–8.

Diaper Area Eruptions

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Introduction

Eruptions in the diaper region have diverse origins. This chapter will review eruptions, both common and uncommon, that have major findings in the diaper area not only in neonates but also in young infants (Box 17.1). Many of the conditions listed in Chapter 10 (vesicles, pustules, bullae, erosions, and ulcerations) may be seen or arise in the diaper region. There are diseases that may also involve other areas of the body and coincidentally affect the diaper area that are mentioned but not discussed in detail in this chapter. Tables 17.1–17.3 describe the clinical setting, morphology, distribution, and best method for diagnosing the major conditions causing diaper area eruptions in neonates and infants.

The term ‘diaper rash’ refers to any eruption in the area covered by the diaper. There are eruptions that are directly related to the wearing of diapers; those aggravated by wearing diapers; and those that occur in the diaper region, irrespective of whether diapers are worn or not. The majority of severe eruptions which have been a direct consequence of diapering, are more uncommon in countries where disposable diapers are used. Ethnic and cultural differences related to the practice of diapering newborn infants have evolved over hundreds of years, from swaddling in the middle ages to the high-technology, multilayered disposable diapers of the twenty-first century. These latter practices have led to a marked reduction in the frequency of diaper eruptions, particularly irritant diaper dermatitis (IDD).

Care of the diaper area in the newborn

The diaper area in newborns is exposed to urine and feces and it is a combination of both that causes IDD. Normal care of the perineal area should be aimed at gentle removal of the excreta, frequent change of diapers, and use of a mild emollient (petrolatum) to prevent irritation. Infants should be bathed with a mild soap. In preterm infants or those with a tendency to develop irritant diaper dermatitis, a barrier product should be applied to the diaper area with each diaper change. A study integrating these practices into skin care routines for infants in a neonatal intensive care unit has led to significant improvements, with less dryness, redness, and skin surface damage.¹ Feces should be removed from the skin as soon as possible after soiling. Plain water alone or a very mild soap, with gentle use of a moist cotton washcloth, is sufficient to remove the feces and urine before the area is gently dried. Rubbing should be avoided. Fragrance- and alcohol-free baby wipes are another convenient option. Baby wipes are now universally alcohol free and contain 98% water.

The ideal or perfect barrier product has yet to be formulated. Traditionally, both lipophilic and hydrophilic ointments and

pastes have been used, often combined with zinc oxide. The more lipophilic products may be highly occlusive, whereas the hydrophilic products are more hydrating but function less effectively as a barrier. Pastes such as zinc oxide paste USP (25% zinc oxide, 25% corn starch, 50% petrolatum) are a more effective barrier, but are more adherent and difficult to remove – caregivers may inadvertently irritate the infant’s skin when trying to remove the residual feces and barrier cream. In general, water-in-oil formulations with a lipid content of 50% provide a better barrier than lighter oil-in-water products. Plain petrolatum is recommended for routine use. Soft zinc paste products such as Ihle’s Paste® (Rougier Pharma Canada) or Triple Paste® (Summers Labs, Collegeville, PA) contain a combination of ingredients such as zinc oxide, cornstarch, petrolatum and lanolin, and are excellent, affordable, nonsensitizing products for both prevention and treatment of IDD. Chapter 5 discusses many of the common ingredients in commercial diaper rash products. Talcum or baby powders and products containing boric acid should not be used because of inherent or potential toxicities associated with their use.

Diaper-related eruptions

IRRITANT DIAPER DERMATITIS

Jacquet² gave the first description of diaper dermatitis in 1905. Irritant diaper dermatitis (IDD) does not usually develop during the neonatal period, particularly in the first 3 weeks of life, and eruptions in the diaper area in this age group should be assumed to be due to causes other than irritation until proven otherwise. Onset of IDD is generally between 3 weeks and 2 years of age, with prevalence highest between 9 and 12 months.³ The condition was previously common, affecting 25% of children seen in a clinic for dermatological diseases,⁴ but the incidence has decreased remarkably in Western cultures owing to the advent of disposable diapers. In certain societies, such as China, where diapering has not been a social convention, IDD has been distinctly uncommon until recently, with the adoption of Western diapering practices.

Home laundering of diapers is now uncommon in Western societies: most parents in developed countries diaper their infants with disposable or cloth diapers from a diaper service. Modern superabsorbent disposable diapers have been shown to be more effective than washable cloth diapers in reducing IDD,^{3,5,6} yet it is estimated that 1–2% of the non-biodegradable waste in North American landfills is composed of disposable diapers.

The evolution of disposable diapers from paper to absorbent cellulose centers, to present-day disposables, which contain both an intricate wicking system that prevents backflow and an absorbent gel matrix that can hold 80 times its weight of fluid, has reduced the prevalence of IDD. The most recent advances

BOX 17.1 CAUSES OF DIAPER DERMATITIS**INFLAMMATORY CONDITIONS**

- Irritant diaper dermatitis
- Seborrheic dermatitis
- Atopic dermatitis
- Psoriasis
- Psoriasiform diaper dermatitis with id reaction
- Erosive perianal eruption
- Pseudoverrucous papules
- Granuloma gluteale infantum
- Senna-induced blistering after laxative ingestion
- Allergic contact dermatitis due to diaper components
- Diaper dye dermatitis and 'Lucky Luke' dermatitis

INFECTIONS

- Candidiasis
- Bullous impetigo/staphylococcal scalded skin syndrome
- Perianal streptococcal dermatitis/streptococcal intertrigo
- *Pseudomonas/ecthyma gangrenosum*
- Tinea infection
- Herpes simplex infection
- HPV infection (condylomata)
- Molluscum contagiosum
- Coxsackie viral infection (hand, foot, and 'butt' exanthem)

METABOLIC

- Nutritional abnormalities
- Zinc deficiency
- Acrodermatitis enteropathica
- Acrodermatitis enteropathica-like eruptions
 - Methylmalonic acidemia
 - Propionic acidemia
 - Glutaric aciduria (type 1)
 - Maple syrup urine disease
 - Ornithine transcarbamylase deficiency
- Citrullinemia
- Biotin deficiency
- Holocarboxylase deficiency
- Cystic fibrosis

MISCELLANEOUS

- Langerhans' cell histiocytosis
- Kawasaki disease
- Granular parakeratosis
- Pyramidal perianal protrusion
- Nascent hemangioma
- Lichen sclerosus
- Pyoderma gangrenosum
- Chronic bullous disease of childhood
- Bullous pemphigoid

in disposable diapers include a slow-release petrolatum surface and a breathable outer sheet.

The most important factor in preventing IDD is the frequency and number of diaper changes. Other factors causing IDD include episodes of diarrhea, antibiotic use, and anatomical problems such as short bowel syndrome. Whereas cloth diapers are less efficient at reducing skin wetness, friction and pH, there is a risk that the expense of superabsorbable diapers may prevent parents from changing the diaper sufficiently often, thus contributing to the development of IDD.

Cutaneous findings

IDD presents as erythema on the convex surfaces of the inner upper thigh, the lower abdomen, and buttock areas, the areas most in contact with the diaper. The creases and the suprapubic area in boys are spared (Fig. 17.1). The eruption may become more severe and inflammatory, with yeast colonization, and



Figure 17.1 Irritant diaper dermatitis with characteristic sparing of the folds.



Figure 17.2 (A) Jaquet's dermatitis. Well-demarcated, punched-out erosions, and ulcers primarily on convex surfaces.

enlarging areas of involvement, including the creases. In more severe cases, the erythema may be accompanied by a glistening or glazed appearance and a wrinkled surface.

Jaquet's erosive dermatitis presents with well-demarcated punched-out ulcers and erosions (Fig. 17.2A,B). It is seen less commonly with the use of disposable diapers, and has usually been associated with infrequent diaper changes and poor removal of chemicals used in home laundering. It may also be seen in infants who have short bowel syndrome or following surgery for Hirschsprung disease, which may result in chronic diarrhea.

Etiology and pathogenesis

At birth, a newborn's skin undergoes a sudden transition accompanied by drying and cooling of the skin surface as it adapts to its new environment.⁷ Visscher⁸ has measured the changes in the newborn's epidermal barrier properties over the first 4 weeks of life, showing increased surface hydration, less transepidermal water movement under occlusion, and a decrease in surface pH. Diapered and non-diapered sites are indistinguishable at birth, but over the first 2 weeks of life diapered areas show consistently increased pH and hydration, thus setting the stage for IDD.



Figure 17.2 (B) Jacquet's dermatitis. Well-demarcated erosions, primarily on convex surfaces.

TABLE 17.1 Eruptions where the diaper/diaper environment is a central cause

Disease	Usual age	Skin: morphology	Skin: usual distribution	Clinical: other	Method of diagnosis/findings
Irritant diaper dermatitis	Between 3 weeks and 2 years. Peak ages 9–12 months	Erythema, with fine scaling and glazed skin surface. Erosions and ulcerations when severe	Convex surfaces of upper inner thigh, lower abdomen and buttock; spares intertriginous creases	Risk factors: cloth diapers, diarrhea	Clinical
Erosive perianal eruption	Usually infants 6 weeks to 3 months of age	Well-demarcated erosions and superficial ulcerations, 0.5–1.5 cm	Perianal skin, opposing areas of buttocks	Associated with frequent stooling of any etiology	Clinical
Pseudoverrucous papules	Usually infants rather than newborns	Well demarcated dome-shaped papules 2–10 mm, with shiny, smooth red or white surface	Perianal region, buttocks, vulvar, scrotal, or around enterostomal openings	Severe, intractable diarrhea from any cause; short gut syndrome, following surgery for imperforate anus or pull through for Hirschsprung disease. May mimic condylomata clinically	Usually clinical Biopsy shows reactive acanthosis or psoriasiform spongiotic dermatitis
Granuloma gluteale infantum	Usually infants rather than newborns	Oval red-brown to violaceous dermal papules or nodules 5 mm to 2–3 cm. Lesions run parallel to skin lines	Perianal, perivulvar or gluteal surfaces of the diaper region. Rarely inguinal folds, neck and axillae	Usually a history of chronic diaper eruption treated with multiple products, including fluorinated steroids	Clinical Biopsy shows dense superficial and deep inflammatory infiltrate composed of lymphocytes, histiocytes and plasma cells, proliferation of dermal blood vessels and extravasated red blood cells and hemosiderin
Granular parakeratosis	Usually 9–22 months of age	Asymptomatic, geometric, yellow brown, scaling plaques with underlying erythema	Areas of friction and pressure in diaper region. May involve axillae	None	Clinical Biopsy shows abnormal keratinization and retention hyperkeratosis
Infantile seborrheic dermatitis	First 4–6 weeks of life, but any time in the first year	Erythematous, well-demarcated patches involving the creases; may affect entire diaper region. Scale often minimal in diaper region	Multiple areas may be involved, especially scalp, eyebrows, sides of nose, axillae, chest, and diaper region	Generally happy babies, unlike infants with AD, who have more pruritus	Clinical KOH to rule out associated candidiasis
Psoriasis	Under 2 years	Brightly erythematous, well-demarcated patches and plaques typically with absent or thin white scale	Often starts on convex surfaces, may affect entire diaper region including creases, gluteal cleft; may also involve face, scalp, trunk, and umbilicus	Eruption often asymptomatic and unresponsive to usual diaper dermatitis treatments	Clinical ± Skin biopsy shows epidermal acanthosis, parakeratosis dilated capillaries
Candidal diaper dermatitis with psoriasiform id reaction	Usually infants 6–24 months but may occur earlier	Initial candidal diaper rash with erythematous patches and peripheral satellite papules or pustules with associated papules and scaly plaques elsewhere on the body	Typical (usually severe) eruption in the diaper area followed by rapid onset of papules and plaques involving the torso, face, less prominent on extremities	Usually asymptomatic; occasionally pruritic	Clinical KOH+ pseudohyphae and spores in diaper region early on
Allergic contact dermatitis	Usually after 6 months of age	Erythema and small vesicles leading to area of eczematous eruption of red papules and vesicles overlying areas of edema	Depends on contact allergen involved: diaper dye dermatitis at margins of diaper Entire diaper region if due to applied topical products	Associated pruritus	Clinical Biopsy shows spongiotic dermatitis with eosinophils
Senna-induced blistering	Usually less than 5 years	Diamond-shaped erosions/ulcerations along the buttocks, linear borders aligning with the diaper edge	Sparing of the perianal area and gluteal cleft	History of ingestion of senna-containing laxatives (e.g., Ex-Lax®) 24 h before lesions appeared May be misdiagnosed as child abuse	Clinical History of diarrhea, recent senna ingestion in infant or child

TABLE 17.2 Infectious causes of diaper area eruptions

Disease	Usual age	Skin: morphology	Skin: usual distribution	Clinical: other	Method of diagnosis/findings
Candidiasis	Common after 2 months of age	Beefy-red eruption emanating from folds with satellite pustules or erythematous eruption extending over perineum with peripheral scale	Begins in inguinal folds, may involve entire perineum	Often history of preceding antibiotic use or diarrhea preceding eruption May have associated oral thrush	Clinical KOH and culture positive for <i>Candida</i>
Impetigo	Often in first few weeks of life	Single or multiple flaccid bullae or moist superficial erosions	Often starts in umbilical stump; spreads to intertriginous areas of diaper region	Usually no other symptoms but neonates with hematogenous spread may develop septicemia, osteomyelitis or septic arthritis	Clinical Gram stain, culture Biopsy rarely required but shows subcorneal pustule
Perianal/perineal bacterial dermatitis	Usually after 6 months of age, more common in toddlers	Moist, bright red erythema around perianal skin with yellowish sticky exudates at periphery. May have small pustules in surrounding skin	Perianal skin most common but can be in inguinal creases, other body folds	Local pain and tenderness common, fever rare. May have concomitant streptococcal pharyngitis. May be trigger for guttate psoriasis	Clinical Culture positive for <i>Staphylococcus aureus</i> or <i>B-Hemolytic Streptococcus</i> spp.
Ecthyma gangrenosum	Usually seen in very premature or immunocompromised infants	Erythematous macule that rapidly evolves into grey nodule, necrotic bulla or ulceration with surrounding bright red areola	May occur anywhere but 50% occur in perineal/gluteal area	Associated neutropenia common May rarely occur in diaper region in normal infants	Clinical Gram stain and culture of lesions or +blood culture
Tinea corporis in diaper area	Usually seen in toddlers	Erythematous scaling papules and plaques with border in diaper region. Deeper follicular papules and pustules in chronic cases	Buttocks, thighs and lower abdomen but may involve entire diaper area	Often family history of tinea pedis or other tinea infection	Clinical KOH and culture+ for dermatophyte, usually <i>T. rubrum</i> or <i>T. mentagrophytes</i>
Herpes simplex	Presents 2–8 days after contact with infected individual	Grouped 2–3 mm umbilicated vesicles and erosions on erythematous base	Neonatal HSV may present on buttocks after breech delivery	Fever and regional adenopathy	Clinical +HSV culture or DFA or PCR. +Tzanck smear of base of vesicle
Condylomata acuminata	Usually seen through vertical transmission from an infected mother; incidence in young infants from child abuse unknown but low	1–3 mm flesh-colored papules that may coalesce to form plaques. Verrucous to velvety surface	May occur on any part of the perineum	Usually asymptomatic	Clinical HPV serotyping available
Molluscum contagiosum	Rare in neonates, increasingly common in toddlers and early childhood	Umbilicated flesh-colored or pink papules, usually several, occasionally large numbers	Often in folds or areas of friction	May have associated molluscum dermatitis	Clinical or biopsy if diagnostic uncertainty
Coxsackie viral infection	1–4 years of age	Small red macules that rapidly evolve into superficial ovoid vesicles on hands and feet. Small papules and superficial erosions seen over buttocks and thighs	Hand, foot, and 'butt' (diaper area) exanthem with erosions and vesicles of buccal area, tongue, gingiva and anterior tonsillar pillars	Fever and malaise Rarely, encephalitis, aseptic meningitis, myocarditis Enterovirus 71 causes pulmonary hemorrhage	Clinical Viral culture or PCR CVA6 prevalent in recent outbreaks often with confluent diaper involvement

TABLE 17.3 Eruptions with accentuation in diaper area irrespective of presence of diapers/diaper environment

Disease	Usual age	Skin: morphology	Skin: usual distribution	Clinical: other	Method of diagnosis/findings
Zinc deficiency/acrodermatitis enteropathica (AE)	True genetic AE occurs within 3 months after weaning; Zn deficiency common in breast-fed premature infants within 1–2 months of age	Crusted, scaling, eczematous to psoriasiform dermatitis. Face and diaper area	Periorificial, perineum, acral and periungual areas	Irritability, diarrhea, sparse hair, recurrent candidal infections especially paronychia, failure to thrive	Clinical Low serum zinc Low alkaline phosphatase
Cystic fibrosis	Infancy	Periorificial and truncal dermatitis	Similar to AE	Significant edema, diarrhea, irritability, alopecia, failure to thrive	Clinical Sweat chloride test CFTR mutational analysis
Langerhans' cell histiocytosis	Birth–4 years	Single, few or multiple lesions. Morphology may vary: yellow-brown papules, nodules, vesicles, erosions, ulcerations, atrophy, palpable petechial lesions, purpura, scale or crusting either alone or in combination	Folds of diaper region characteristic, also trunk, scalp and retroauricular regions	Gums, teeth and nails may be involved Bony involvement in 50%; lymphadenopathy 14%; liver or CNS in 10% (diabetes insipidus)	Clinical Confirm with skin biopsy showing infiltrate of CD1A+ cells in epidermis and dermis
Pyramidal perianal protrusion	Usually 1–30 months of age	Pyramidal shaped soft tissue 'tag-like' protrusion – occasionally has a tongue-like lip	Seen in midline of perineum typically anterior to the anus but can be at other locations. Perianal, perivulvar and buttocks, may occur on lip or perioral region	Often a history of constipation or diarrhea. May be associated with lichen sclerosis (LS) Associated pain, occasionally secondary infection. Concern for spinal dysraphism/urogenital anomalies with very large lumbosacral lesions	Clinical Biopsy shows normal skin unless LS changes present (rarely required)
Nascent ulcerated infantile hemangioma	Birth to a few days of life	Oval to annular area of superficial to full thickness skin ulceration. Often surrounding telangiectasia or tiny vascular papules			Clinical Hemangioma becomes evident over next few days to weeks.
Lichen sclerosus	Usually in childhood 5–7 years, but may be seen in infancy	White, glistening, atrophic changes in the vulvar area and perianal skin. Associated purpura, and small hemorrhagic vesicles may be seen	Figure-of-eight distribution in perineum. Phimosis in boys; rarely extragenital lesions	Associated pain, itching, dysuria constipation and encopresis may be present	Biopsy: Glut-1 + vessels Clinical Biopsy confirms (rarely necessary)
Pyoderma gangrenosum	Uncommon in infancy but reported as young as 3 months	Tender papulopustule rapidly evolves into undermined ulcer with violaceous border. Rarely bullous and hemorrhagic	Head and anogenital sites most common in infants and children. Lower extremities in older children	Painful, usually associated with IBD, also seen in immunodeficiency, leukocyte adhesion defect, leukemia, rheumatic disorders	Clinical Biopsy not specific but helpful to exclude other disorders, i.e., infectious ulcers and vasculitis
Chronic bullous disease of childhood	Usually in early childhood. Rare in infancy	Annular to polycyclic vesicles and bullae forming rosettes or 'string of pearls'	Diaper area, buttocks and inner thighs characteristic with spread to the trunk and scalp and face	May present initially with fever or other constitutional symptoms	Clinical Confirm with biopsy: subepidermal blister with polys and eosinophils Immunofluorescence +linear IgA deposits
Bullous pemphigoid	Rare in infants and children but earliest reported case 2 months of age	Urticarial papules and plaques evolve into tense, often hemorrhagic bullae 0.25–2 cm in size. Blisters on normal or inflamed skin	Widespread distribution, often involves perineum, flexures of limbs and face; mucosal involvement may occur in older children	Associated itching and pain	Clinical Confirm with biopsy, subepidermal blister with eosinophils Immunofluorescence, deposits of C ₃ and IgG at BMZ
Kawasaki disease	Infancy to 5 years	Eruption may be polymorphous; often involves diaper region in young infants, with perineal erythema, small sterile pustules, urticarial lesions, early evidence of desquamation in perineal area	Accentuation in perineal area but can be widespread macular scarlatiniform, or maculopapular lesions	Persistent fever, irritability, conjunctivitis, strawberry tongue, fissured lips, cervical adenopathy, peripheral edema, leukocytosis, thrombocytosis, increased ESR, sterile pyuria, pericardial effusions and myocarditis Can be familial or sporadic	Diagnostic clinical criteria Echocardiogram
Clear cell papulosis	Infants to toddlers	Small hypopigmented macules, flat-topped papules	Diaper area, abdomen, milk line		Biopsy shows large clear cells within the lower epidermis, PAS+



Figure 17.3 (A) Erosive perianal eruption in an infant with chronic diarrhea. (Courtesy of A. Torello, MD.)

IDD results from the interaction of several factors associated with prolonged contact of the skin with a combination of both urine and feces (Tables 17.1–17.3). The wearing of diapers causes a significant increase in skin wetness and pH.⁹ Prolonged wetness leads to maceration of the stratum corneum due to disruption of the intercellular lipid lamellae.¹⁰

Weakening of the stratum corneum from excess hydration makes the skin more susceptible to damage by friction from the diaper. Fecal lipases and proteases are activated by the increased pH in the urine.¹¹ In addition, the acidic pH of the skin surface is essential for maintaining a normal cutaneous microflora, which protects against invasion by pathogenic bacteria and yeasts.¹² When diarrhea occurs, the fecal lipases and proteases increase in the diaper, leading to further damage to the stratum corneum. In the etiology of primary IDD, ammonia and *Candida* play less of a role than previously thought.

Differential diagnosis

Ordinarily the diagnosis is straightforward and uncomplicated. Many of the disorders listed in Box 17.1 present with subtle differences from IDD, particularly psoriasis and allergic contact dermatitis. Atopic dermatitis (AD) classically spares the diaper region, but infants with widespread AD may have involvement of the skin just above the margin of the diaper. Strict attention to the morphology and location of lesions, the absence of pustules or vesicles, and the absence of lesions in the creases should lead the physician to the correct diagnosis.

Treatment and care

Evidence-based practice guidelines for care of diaper dermatitis in hospitalized patients has reduced prevalence in high risk units.¹³

Mild topical steroid therapy (1% hydrocortisone ointment) covered by a barrier product three times daily, will clear the majority of IDD that does not respond to barrier products alone. The use of potent fluorinated topical steroids in the diaper region is not recommended as the natural occlusion of this area will promote increased absorption and may cause atrophy, striae, and adrenal suppression. When the practitioner is faced with a severely inflamed recalcitrant dermatitis in the diaper area, it is safe to use a week-long course of a medium-potency topical steroid to bring the eruption under control. The role of topical immunomodulators in the management of



Figure 17.4 (A) Extensive perianal pseudoverrucous papules. (B) Extensive pseudoverrucous papules in an infant with congenital genitourinary anomalies and chronic urinary leakage.

diaper dermatitis is unclear and cannot be recommended until further data are available on their safety and use in infants under 2 years of age.

EROSIVE PERIANAL ERUPTION

This entity presents with erosions and ulcers in the perianal skin and occurs most commonly between 6 weeks and 3 months of age, but can be seen at other ages. The etiology is almost universally associated with frequent stooling, either in breast-fed babies, children with diarrhea due to malabsorption, or infection in infants with short gut syndrome (Fig. 17.3A,B). This condition may eventuate into pseudoverrucous perianal papules in infants who undergo enterostomal closure, or following pull-through surgery for Hirschsprung disease.¹⁴ In mild cases, frequent diaper changes and use of a barrier product such as zinc oxide or triple paste with a low- to medium-strength topical steroid ointment applied two to three times daily, is helpful. In patients with short gut or other malabsorption syndromes the condition may be chronic, unremitting, and very difficult to treat. Incorporation of potato-derived protease inhibitor into a diaper barrier product has improved control of dermatitis in a small cohort of patients following colon resection for long-segment Hirschsprung disease.¹⁵



Figure 17.3 (B) Erosive perianal eruption. (Courtesy of A. Torrelo, MD.)



Figure 17.5 Granuloma gluteale infantum. Larger violaceous nodules are evident.

PSEUDOVERRUCOUS PAPULES

Pseudoverrucous papules (PVP; sometimes referred to as ‘pseudoverrucous papules and nodules’), and granuloma gluteale infantum, the more severe forms of Jacquet’s erosive diaper dermatitis, are probably best viewed as reaction patterns following chronic, unremitting irritation due to feces, urine, or a combination thereof.¹⁶ Pseudoverrucous papules were first described by Goldberg and colleagues^{17,18} in the setting of chronic diaper dermatitis, encopresis or peristomal skin irritation.

Well-documented precipitating factors leading to this condition include chronic diarrhea due to malabsorption, short-gut syndrome, or surgical repair of Hirschsprung disease or imperforate anus; leakage around stomas (either urinary or fecal); and chronic incontinence. Clinical features include dome-shaped papules, typically varying in size from 2 to 10 mm, often with a shiny, smooth, white or red surface (Fig. 17.4). Biopsy specimens reveal reactive acanthosis or psoriasiform spongiotic dermatitis. The lesions regress when the irritating factor is removed. Recognition of this entity is important because pseudoverrucous papules and nodules may mimic other dermatoses, especially condyloma acuminatum, and unnecessary work-up for sexual abuse may be initiated.

GRANULOMA GLUTEALE INFANTUM

Granuloma gluteale infantum (GGI) was originally described by Tappeiner and Pfleger.¹⁹ It is rarely seen today and there are only 30 cases reported in the literature. Infants present with oval red-brown-purple dermal nodules on the gluteal surface and diaper area (Fig. 17.5).^{20,21} Rarely, lesions may be present in the intertriginous areas, including the neck and axilla. The long axis of the lesions runs parallel to skin lines. In the majority of affected infants there is a history of a preceding eruption in the diaper region treated with fluorinated topical steroids. Similar granulomas in the diaper region have been noted in adults who are incontinent or confined to bed.²² The etiology of GGI is unclear, but some have hypothesized that it is a skin response to the combined effects of inflammation, maceration, local infection with *Candida*, and use of fluorinated steroids. The sparing of deep folds suggests that occlusion by the diaper is necessary for its formation.



Figure 17.6 Blistering of the buttocks and perineum after accidental ingestion of senna-containing laxative. (Courtesy of Beth Drolet, MD, and reprinted with permission from Spiller HA, Winter ML, Weber JA, Krenzelok EP, Anderson DL, Ryan ML. Skin breakdown and blisters from senna-containing laxatives in young children. *Ann Pharmacother* 2003; 37(5):636–639.)

As for all forms of irritant diaper dermatitis, treatment should be directed at correcting the underlying cause of the chronic urine or fecal leakage whenever possible, as well as frequent use of a barrier product. Lesions generally resolve completely and spontaneously after a period of several months if the source of chronic irritation can be removed.

SENNA LAXATIVE-INDUCED BLISTERING DERMATITIS IN TODDLERS

Phenolphthalein was removed from all over-the-counter laxatives in 1999 and replaced with senna, an ornamental plant-derivative containing multiple anthraquinones. In a review of data from six poison centers in 2002, of 111 children less than 5 years of age who accidentally ingested senna-containing laxatives, 33% experienced severe diaper rash.²³ The eruption is seen in infants or toddlers wearing diapers or pull-ups after overnight contact of the skin with large loose stools following accidental ingestion of chocolate squares of senna-containing laxatives. Therapeutic use of senna in a 3-year-old child with Hirschsprung disease and a pull-through procedure produced a similar eruption.²⁴ This severe irritant contact dermatitis presents with distinct features, including a diamond-shaped lesion along the buttocks, linear borders aligning with the diaper edge, with usual sparing of the perianal area and gluteal cleft.²⁴ Patients with this entity may be initially misdiagnosed with abusive scald burns (Fig. 17.6).

GRANULAR PARAKERATOSIS

Granular parakeratosis is a rare disorder of keratinization characterized by retention hyperkeratosis. Its precise etiology is unknown, but it is generally viewed as a reaction to chronic irritation or possibly as a reaction to certain topical products such as zinc oxide, which are commonly used in the diaper area. It was originally described in the axillary region of adults, but there have recently been several reports in infants 9–22 months of age.



Figure 17.7 Granular parakeratosis. (Courtesy of Dr Julie Prendiville.)

Infants usually present with asymptomatic, geometric yellow-brown, superficial scaling plaques with pronounced underlying erythema²⁵ in areas of friction and pressure in the diaper region. A second pattern of linear warty papules in the inguinal area has also been described (Fig. 17.7).²⁶

The cause of this peculiar entity is obscure, but immunohistochemical and electron microscopic studies suggest that there is a defect in the processing of profilaggrin to filaggrin, which results in failure of the normal degradation of keratohyalin and clumping of keratohyalin filaments during cornification.²⁷ These abnormal components result in the retention hyperkeratosis seen. Friction, moisture, and occlusion from diapers may trigger defective maturation of the stratum corneum at local sites in susceptible infants.

Treatment is empiric, with variable response to topical steroids, calcineurin inhibitors, calcipotriene cream, keratolytics, and emollients.^{25,28} The majority of cases clear spontaneously after months, but occasionally patients may have lesions for several years.

INFANTILE SEBORRHEIC DERMATITIS (ISD)

First described by Unna in 1887,²⁹ ISD (see also Chapter 15) is a disease that affects infants usually in the first 2 years, with a distinct inflammatory eruption that primarily involves the scalp, retroauricular area, face, chest, diaper, and intertriginous areas. A precise definition is lacking; some physicians confine the entity to the presence of scalp scaling without inflammation called 'cradle cap' that affects the vertex of the scalp, whereas others only use the term if there is inflammation of the scalp and in other seborrheic sites.

Cutaneous features

The eruption usually begins under 6 weeks of age, but may occur up to 1 year or even later.³⁰ Both sexes are equally affected. The vast majority of infants develop cradle cap alone; this is a collection of asymptomatic, greasy keratin on the vertex of the scalp (retention hyperkeratosis), without inflammation or involvement of other areas. A few patients develop multiple areas of involvement, including erythematous well-demarcated patches in the retroauricular area, eyebrows, along the sides of the nose, and involving the axillae, chest, and diaper area. The most commonly involved areas are the scalp and diaper area



Figure 17.8 (A,B) Seborrheic dermatitis involving the diaper area and scalp.

(Fig. 17.8). Although there is often a yellow, greasy scale on the erythema, this is not invariably present and is usually absent in the diaper area, where lesions consist of erythematous, well-demarcated patches involving the creases, but sometimes affecting the whole region. Scale is unusual or minimal in the diaper area. If there is invasion by *Candida albicans*, crusting and scaling may occur.³¹

Differential diagnosis

It is sometimes difficult to differentiate ISD from atopic dermatitis (AD). The scalp is often involved in both conditions; the pruritus with AD may not be evident early in infancy, and occasionally, ISD may be pruritic. The flexures are frequently involved in both conditions, although the antecubital and popliteal fossae are more commonly involved in AD and the axillae in ISD. Distinguishing features include xerosis of the skin and sparing of the diaper area in AD. Psoriasis in the diaper area is now more frequently recognized in infants, and is at times impossible to distinguish from ISD. The lesions are often confined to the diaper area as well-demarcated, erythematous and

glistening plaques, with a thin, white scale. Infants seldom have the thick silvery scale that is normally seen with psoriasis in other areas. The typical inflammatory areas seen in ISD are absent in psoriasis.

Langerhans' cell histiocytosis (LCH) is a potentially lethal disease that can mimic ISD in the diaper area and scalp. Unlike ISD, LCH lesions are crusted, ulcerative, petechial, and purpuric.

IDD usually spares the creases, and other eruptions in the diaper area have specific presentations that allow distinction from ISD.

Etiology and pathogenesis

The etiology of ISD in infants is probably the result of colonization and proliferation of the yeast *Malassezia furfur* (*Pityrosporum ovale*).³² *Malassezia* organisms thrive in an oily environment and may proliferate more in those infants whose hair is only shampooed once or twice a week, or who have emollients applied to the scalp. There is a marked decrease in the incidence of IDD in those infants whose hair is shampooed on a daily basis. A familial tendency may be relevant.³³ Other theories of causation, including biotin and essential fatty acid deficiency, have not been proved.³⁴

Prognosis and treatment

The majority of infants are cured within 2–4 weeks of treatment without recurrence³⁵; and the relationship to adult disease is not known.³³ Cradle cap can be treated with simple measures, including washing the scalp daily with a mild shampoo (Johnson's Baby Shampoo®) following the application of oil (mineral oil, Aveeno oil®) to loosen the scale. A mild topical steroid cream (hydrocortisone 1%) three times a day may be necessary if there are inflammatory lesions. The etiology of ISD is thought to be an infection with a yeast organism, and antifungal measures have proved to be as effective as topical steroids.³⁶ An antifungal shampoo (ketoconazole) daily, followed by the use of ketoconazole cream three times a day, is effective in treating the condition.

PSORIASIS

Psoriasis is a common chronic inflammatory skin disease that affects adults and children. It is characterized clinically by typical scaly plaques, and pathogenetically by an accelerated epidermal cell turnover. The condition is being increasingly recognized in early infancy, and often affects the diaper area, particularly in those under 1 year.³⁷ Of the one-third of cases of psoriasis that occur before age 20, 2% occur before the age of 2.³⁸ There is often a family history of psoriasis in infants and children who develop the disease.³⁸

Cutaneous findings

Caregivers complain of an eruption in the diaper area that is asymptomatic but unresponsive to standard treatment. Lesions appear as erythematous, glistening, well-demarcated patches with a thin white scale, or they affect the whole diaper area including the creases (Fig. 17.9A–C,D).³⁹ Other areas are less frequently involved and include the face, scalp, trunk, and umbilical areas, with erythematous papules and plaques. The scale is often thin and lacks the characteristic silvery scale seen in older children and adults. Guttate lesions and nail changes are rare in infants.

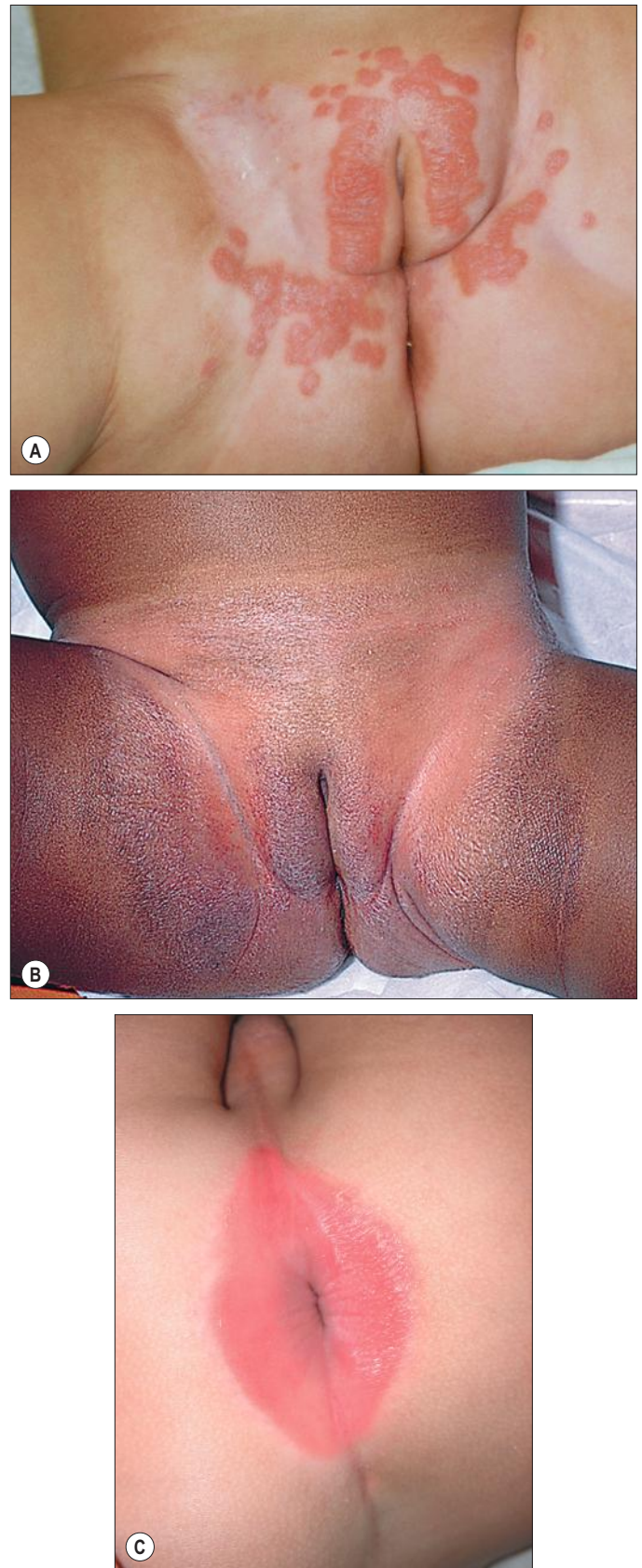


Figure 17.9 (A,B) Psoriasis. Typical diaper involvement. (C) Perianal psoriasis in a toddler.

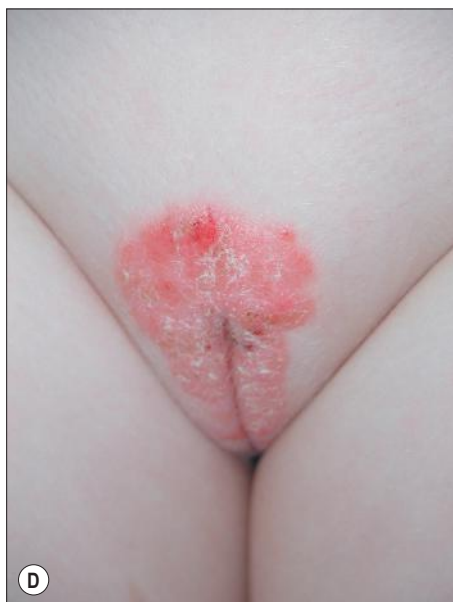


Figure 17.9 (D) Vulvar psoriasis in a toddler.

Although pustular psoriasis may occur in infancy, it does not affect the diaper area specifically. Patients present with fever and malaise, associated with either small pustules on an erythematous base or annular erythema with peripheral pustules. Occasionally, coalescence may lead to the formation of lakes of pus on the skin surface.

Extracutaneous findings

It is increasingly recognized that psoriasis may be associated with internal organ involvement. Joints are affected in 10% of patients, although this is uncommon in infancy. Geographic tongue may be seen, particularly in pustular variants. There is a small but well recognized increase of psoriasis in patients with Crohn disease. Patients with acute pustular psoriasis may develop a sterile osteomyelitis, and there have been a few reports of lung involvement in acute-onset psoriasis.

Differential diagnosis

At times it may be extremely difficult to distinguish between ISD and psoriasis. Many of the patients diagnosed with ISD who develop psoriasis later in life probably had psoriasis at the outset. Psoriasis is more chronic and more resistant to treatment, and usually spares the flexural areas, which are commonly involved in ISD. The umbilical area is commonly involved in both conditions, but particularly in psoriasis. Resolution of psoriasis in infancy is often very rapid, unlike in older children, adding to the difficulty of distinction from ISD. The lesions of atopic dermatitis are pruritic, poorly demarcated, and usually spare the diaper area.

IDD lesions have a typical pattern, spare the creases, and are not as well demarcated as those in psoriasis.

Etiology and pathogenesis

There is a strong genetic component in patients with psoriasis, particularly in the younger age groups.⁴⁰ The pathogenesis of psoriasis is thought to involve an imbalance of T-helper cells resulting in a Th1-type cytokine reaction pattern. In addition, the cell turnover period is increased to 4 days in psoriasis, in comparison to a normal cell turnover period of 28 days.

Prognosis and treatment

The outcome of psoriasis in the younger age group is unknown. Many cases only have a single outbreak, others become chronic with frequent flares, and there are some patients who have a diagnosis of ISD or psoriasis in infancy who develop psoriasis many years later.

Daily bathing followed by the application of a mild topical steroid cream or ointment (hydrocortisone 1%) to the affected areas of the face and diaper area, and a moderate steroid ointment (triamcinolone) to the affected body areas three times a day, usually produces a rapid resolution of the lesions. If a mild steroid ointment is not sufficient to cause regression, a short trial of a medium-strength topical steroid in the diaper area may be given for a few weeks. It is important not to use anything stronger, as striae, atrophy, and iatrogenic Cushing syndrome have resulted from the use of potent topical steroids under the occlusive environment of the diaper. If complete regression is not seen within 3–4 weeks, a refined tar product, liquor carbonis detergens (LCD), can be compounded with the steroid in a 5–10% concentration. Salicylic acid is not recommended in neonates and infants, as systemic absorption can lead to salicylism.

CANDIDAL DIAPER DERMATITIS WITH PSORIASIFORM ID

This condition was first described in the 1960s as ‘diaper dermatitis with psoriasiform id.’⁴¹ It consists of a candidal eruption in the diaper area, followed a few days to weeks later by an explosive psoriasiform eruption on other areas of the body. It has been seen much less frequently in recent years.

Cutaneous findings

The condition usually affects infants between 6 and 24 months, but may occur earlier. The sexes are equally affected. There is an initial infection with *Candida albicans* in the diaper area⁴² that is severe, prolonged, or inadequately treated. The diaper lesions are erythematous patches with a peripheral scale, typical of *Candida albicans* in that area. Days to weeks later, often soon after the initiation of effective therapy of the diaper rash, there is an acute explosion of lesions anywhere on the body and face that consist of well-demarcated psoriasiform plaques (Fig. 17.10).⁴³

Etiology and pathogenesis

The exact etiology of the psoriasiform id reaction is unknown. Id (also known as auto-eczematization) reactions occur in conjunction with several other infectious and inflammatory diseases, including tinea capitis and pedis, but the pathogenesis of the id reaction remains obscure. Some infants may have a genetic predisposition to developing psoriasis.

Prognosis and treatment

Lesions on the face are treated with a low-potency topical steroid cream 2–3 times a day, those on the body with a mid-potency topical corticosteroid cream 2–3 times a day, and those in the diaper area with an antifungal agent, usually a topical imidazole, 3–4 times a day. Cure occurs within 4–6 weeks and there is no recurrence, although there have been some reports of psoriasis developing some years later.⁴¹

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis (ACD) may occur in the diaper region after exposure to fragrances, dyes, other components of the diaper itself, or to products applied by the caregivers to



Figure 17.10 *Candida* with psoriasiform id. Note that lesions extend onto areas distant from the site of the diaper rash.



Figure 17.11 'Lucky Luke' allergic contact dermatitis from disposable diaper components.

diapered skin.^{44,45} Weston and Weston⁴⁶ showed that ACD may account for up to 20% of all cases of childhood dermatitis, refuting the notion that ACD is rare in children. Sensitization may begin as early as 6 months of age.⁴⁷ Allergens to which infants and children have become sensitized include urushiol (poison ivy), nickel (in metal snaps on clothing), thimerosal, neomycin, chromates, Balsam of Peru, and formaldehyde and related preservatives.⁴⁸

A specific form of ACD on the outer buttocks and hips was determined by patch-testing to be due to rubber components in the elastic bands of the diapers. The authors termed this entity 'Lucky Luke dermatitis' after the cartoon character who carries his gun holster in the same area (Fig. 17.11).^{49,50} Recently, Alberta and coworkers⁵¹ reported several infants with ACD caused by the various blue, pink, and green dyes used in diapers. Changing to dye-free diapers quickly alleviated the rash.

ACD may be present in the same areas of the diaper as IDD, but the morphology of the lesions is different in ACD, beginning with erythema and small vesicles and leading to an eczematous eruption with red papules or vesicles overlying areas of edema.⁴⁴ Treatment with a medium-strength topical steroid provides rapid relief of symptoms, but removing the offending allergen is key to preventing recurrences.

Infections

CANDIDIASIS

Candidiasis (yeast infection) (see Chapter 14) caused by the yeast *Candida albicans*, is the most common infection in newborns.⁵² Some 3% of infants are affected from the 2nd to the 4th month of life.⁵³ Thrush (oral candidiasis) is common in early infancy, probably owing to infection from the mother's vaginal canal. Candidiasis may be congenital, occurring in the first week of life through an ascending infection. Candidiasis usually affects the skin and mucous membranes only, but in certain circumstances, such as low birthweight or with systemic infections around the birth period, invasive systemic disease particularly affecting the lungs may occur.



Figure 17.12 *Candida* diaper dermatitis. (A) A toddler with classic bright red papules surrounded by a collarette of scale. (B) An infant with involved skin folds and satellite papules.

Clinical picture

In congenital candidiasis, lesions may occur anywhere, including the face, feet and hands; the diaper area is not particularly involved. Occasionally, the nails may be hypertrophic. The lesions are erythematous papules and sheets of erythema, and are present soon after delivery, beginning at birth or in the first week of life. Candidal diaper dermatitis usually begins around 6 weeks of age and is seldom seen before this time. It is common to have a history of antibiotic use or diarrhea preceding the appearance of the eruption.

The entire perineal area, including the creases, may be affected. The morphology of the lesions takes two forms: a diffuse erythematous patch extending over the perineum with a peripheral scale, or small pink papules surmounted by a scale, and coalescence in some areas (Fig. 17.12A,B,C). The more classic picture of a beefy-red diaper area with satellite pustules (Fig. 17.12B) is less common, possibly because of earlier treatment with antifungal agents. Infants should be examined for evidence of oral candidiasis (thrush), which typically presents as small white patches on the buccal mucosa.

Differential diagnosis

In IDD, the creases are spared. Perianal *Streptococcus* infection appears as painful, beefy-red lesions surrounding the anus. ISD



Figure 17.12 (C) Candidal diaper dermatitis in a less severely affected infant with involved skin folds and satellite papules.

presents with erythematous patches: it does not have the peripheral scale or the satellite papules or pustules seen in candidiasis.

Etiology and pathogenesis

In congenital candidiasis, there is an ascending infection causing a chorioamnionitis whereas in neonatal candidiasis, the lesions are formed when *Candida albicans* is excreted in excessive amounts in the feces. This is often preceded by the use of antibiotics and diarrhea of any cause. The significance of recovering *Candida albicans* from the diaper area is difficult to interpret, as the organism may be recovered in any irritant skin condition in the diaper area after 72 h,⁵⁴ and may even be present in small amounts on normal skin. However, when candidal infection occurs, the organism is present in much larger numbers in the skin and feces.^{55,56} *Candida* has the ability to invade through the epidermal barrier by liberating keratinases.

Prognosis and treatment

In congenital candidiasis, in full-term infants, the prognosis is excellent and treatment is seldom necessary, or a topical antifungal may be warranted. In neonates weighing less than 1000 g, systemic involvement may occur requiring treatment with amphotericin or fluconazole.⁵⁷ Studies comparing the various treatment options for *Candida* diaper dermatitis are lacking.⁵⁸ Treatment with topical anti-candidal therapy, either nystatin (cream or ointment) or one of the imidazoles (clotrimazole, miconazole, or ketoconazole), three times daily, is generally effective in producing resolution in about 2 weeks. A formulation of miconazole 0.25% compounded in zinc oxide and petrolatum (Vusion®, Barrier Therapeutics, Princeton, NJ) has recently been approved specifically for the treatment of documented *Candida* diaper dermatitis.⁵⁹ The use of additional hydrocortisone 1% to one of the above agents provides an anti-inflammatory effect and may promote more rapid resolution of the eruption, but this has not been studied in formal clinical trials. Potent topical corticosteroids should be avoided.

Burow's solution (5% aluminum subacetate) or normal saline compresses may be useful in inflammatory lesions. In a double-blind study, the oral use of nystatin (to eliminate *Candida* from the bowel), in conjunction with topical nystatin did not affect the outcome of the dermatitis more favorably than topical nystatin alone,⁶⁰ however, if oral candidiasis is present, oral nystatin suspension is required both to treat the thrush and to prevent recurrence of the diaper rash. Oral fluconazole (6 mg/kg as a loading dose and 3 mg/kg/day for 1–2 weeks) is very effective in treating mucocutaneous *Candida* infection. However, if topical therapy is ineffective, an alternative diagnosis or the presence of a concomitant immunodeficiency should be considered.

STAPHYLOCOCCAL INFECTION: IMPETIGO/STAPHYLOCOCCAL SCALED SKIN SYNDROME (SSSS)

Impetigo is the most common bacterial skin infection seen in infants and children,⁶¹ and the most common organism causing impetigo in infants is *Staphylococcus aureus*, phage type 2. The diaper area is frequently affected with lesions, which appear as flaccid bullae. A generalized form of staphylococcal infection caused by a number of exotoxins of phage 2 is known as staphylococcal scalded skin syndrome (SSSS) (see Chapter 12). Infants and young children are primarily affected, but the disease has

been reported in adults, usually in immunocompromised patients, in whom there is a sizable mortality rate. The diaper area of the neonate is often affected by SSSS. Very occasionally, a *Pseudomonas* exotoxin may cause lesions that resemble SSSS. *Streptococcus pyogenes* is rarely the sole cause of impetigo in the neonate.

Cutaneous findings

The infection can occur at any time and in any location, but often presents in the first 2 weeks of life in the diaper area. Constitutional signs are absent. The lesions may be single or multiple, and are either flaccid bullae or moist, superficial erythematous erosions (Fig. 17.13A) that have a thin peripheral collarette of scale after the bullae rupture. Initially pus is not present and there is serous fluid in the bullae. After a few days, the fluid becomes cloudy and pus is seen in the dependent area of the bulla. The lesions are superficial and there is no scarring once resolution occurs. A culture from the lesions or the umbilical stump usually yields a heavy growth of *S. aureus*.

SSSS presents with skin findings alone, but occasionally there may be a short prodrome of sore throat or conjunctivitis, followed by the release of toxin. The skin is sensitive to the touch and erythematous, with widespread exfoliation and fissuring

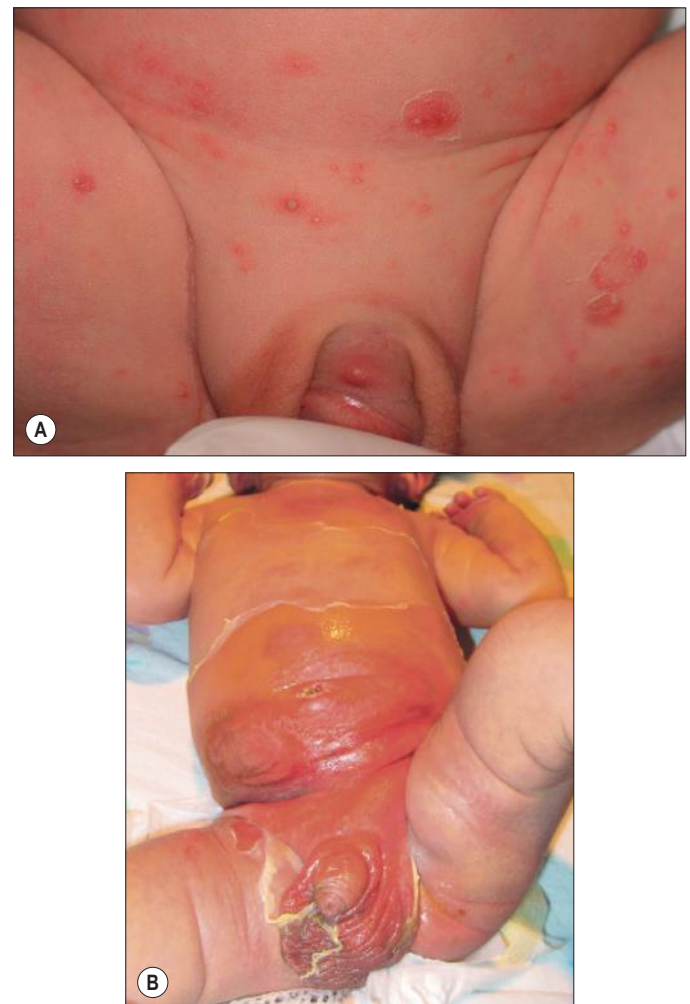


Figure 17.13 (A) Staphylococcal infection with both pustules and bullae in an 11-day-old infant. (B) Staphylococcal scalded skin syndrome in a neonate involving the diaper region.

around the mouth. Areas of involvement can be limited to the neck or diaper area (Fig. 17.13B). The mucous membranes are unaffected. The organisms can be cultured from the nose, pharynx and umbilicus, but not the skin. The Nikolsky sign is positive.

Etiology and pathogenesis

The most common entry point in neonates is an infected umbilical stump. The eruption is caused by *S. aureus* phage type 2. Locally produced exfoliative or epidermolytic toxins A and B bind to desmoglein 1 in the desmosomes, with resultant proteolysis.^{62,63} The toxins cleave the granular layer.⁶⁴ In bullous impetigo, the exfoliating toxin is confined to the area of infection. In SSSS the exotoxin is spread hematogenously from a local source.

Differential diagnosis

It is important to rule out other causes of blistering in the neonate. The most important are herpes simplex infection and epidermolysis bullosa. In herpes simplex infection, the vesicles are grouped and small, whereas in impetigo, they tend to be larger bullae. Erythema toxicum presents with small pustules on an erythematous base, and small pustules are also seen with transient neonatal pustular melanosis, acropustulosis of infancy, and congenital candidiasis. Lesions are often smaller than those seen with impetigo and are pustular, whereas in impetigo the bullae are larger and flaccid or superficial erosions. Other rare causes of bullae in the neonate include pemphigus, pemphigoid, and incontinentia pigmenti, although these do not usually present with large flaccid bullae or erosions, and the diaper area is not specifically involved.

Prognosis and treatment

Both bullous impetigo and SSSS have a good prognosis in infants and children. It is important to treat bullous impetigo immediately to prevent spread in the nursery. Oral antibiotics such as cloxacillin, cephalexin, and erythromycin are all effective as a 10-day course and lead to rapid cure in 5–7 days, with no scarring or recurrence. Some centers use IV antibiotics. In methicillin-resistant cases, it may be feasible to use topical fusidic acid, mupirocin or retapamulin if the lesions are localized.⁶⁵

PERIANAL AND PERINEAL BACTERIAL DERMATITIS

Infections with β -hemolytic streptococci and *Staphylococcus aureus* may take several forms in this region, including perianal dermatitis, intertrigo, cellulitis, vulvovaginitis, and balanoposthitis (see Chapter 12).^{66–68} Honig and colleagues⁶⁹ reported a case series of infants less than 5 months of age with streptococcal intertrigo involving the inguinal, axillae, limbs and neck folds. Perianal streptococcal dermatitis (PSD)⁶⁷ is the most common presentation and is seen more frequently in males. A recent report suggests that there may be a shift occurring in the microbiology of this entity with *Staphylococcus aureus* predominance.⁷⁰

Cutaneous findings

PSD presents as sharply circumscribed perianal erythema with occasional fissures, often with a sticky yellowish exudate that accumulates at the periphery (Fig. 17.14A,B). Pustules may also be present at the border of the lesions. The surface is often



Figure 17.14 (A) Perianal streptococcal dermatitis with guttate psoriasis.

tender to touch, and there are associated symptoms of itching, painful defecation, or blood-streaked stools.

Extracutaneous findings

Infants may present with constipation, pain with defecation, or even encopresis. Fever is rare. Guttate psoriasis, which is typically associated with streptococcal pharyngitis, may be seen with PSD (Fig. 17.14A). Therefore, any patient with new-onset guttate psoriasis should have an anogenital examination and appropriate cultures should be obtained.

Etiology and pathogenesis

The mechanism of infection may be related to tropism of specific GABHS (group A β -hemolytic *Streptococcus*) strains to this area, but colonization may occur through the passage of swallowed GABHS in the gastrointestinal tract, or orodigital contamination from a focus of GABHS pharyngitis.⁶⁸ Communal bathing has contributed to familial outbreaks.⁷¹ Similar clinical presentations have been reported with cultures positive for *S. aureus* strains.

Diagnosis and differential diagnosis

The differential diagnosis includes psoriasis, seborrheic dermatitis, cutaneous candidiasis, pinworm infestation, Crohn disease, and sexual abuse. The diagnosis is confirmed by bacterial culture of the affected area. Certain laboratories may use media selective for enteric pathogens when plating swabs from this area, so it is essential to specifically request isolation of GABHS. If culture is negative but clinical suspicion is high, culture of the pharynx may provide additional evidence for GABHS.

Treatment and care

Treatment with a 10-day course of oral penicillin V or amoxicillin, with or without adjunctive topical mupirocin ointment applied twice daily, is usually curative. Erythromycin may be

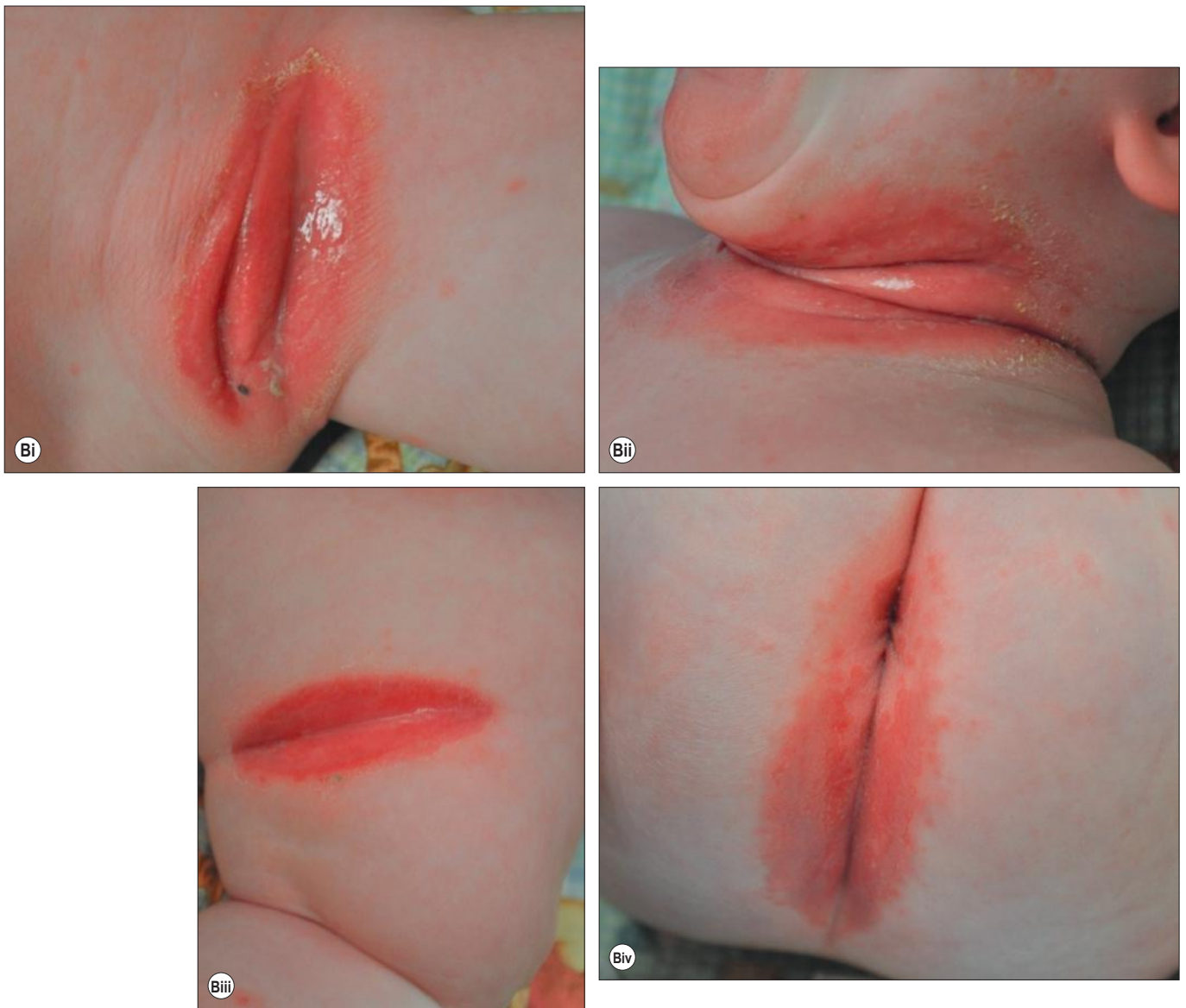


Figure 17.14 (B) Infant with group A streptococcal infection involving perianal and other creases. Moist erythema of the folds is characteristic.

used in penicillin-allergic patients. Recurrent disease may prompt the need for repeated or more prolonged oral therapy. Repeated recurrences are uncommon, but may require strategies similar to those used to eliminate streptococcal carriage from the pharynx.

ECTHYMA GANGRENOSUM

Ecthyma gangrenosum (EG) is due to direct skin inoculation or more commonly to septicemia caused by infection with *Pseudomonas aeruginosa*. It may occur anywhere on the skin surface, but over 50% present in the perineal/gluteal area. It usually occurs in immunocompromised infants but occasionally occurs in healthy children with transient neutropenia from another infection.⁷² Skin lesions begin as an erythematous macule that rapidly enlarges into a gray nodule, necrotic hemorrhagic bulla, or ulceration with a bright red surrounding areola and a central eschar.⁷³ Differential diagnoses include cutaneous anthrax⁷⁴ as well as opportunistic pathogens, including *Aeromonas*, *Aspergillus*, and *Mucor*. Treatment is with anti-pseudomonal systemic antibiotic therapy initiated as soon as possible because of the rapid extension of the disease.⁷⁵

DIAPER DERMATOPHYTOSIS

Dermatophyte infections of the diaper region are rare but often misdiagnosed. Isolated organisms include *Trichophyton rubrum*, *T. mentagrophytes*, and *T. verrucosum*, as well as *Epidermophyton floccosum*.^{76,77} Often other family members, particularly the patient's parent, have associated tinea pedis or cruris. Standard remedies for IDD or the use of topical nystatin (which is efficacious against *Candida* but not dermatophytes) will not alleviate the problem and may exacerbate it. Examination shows annular, erythematous, scaling papules and plaques in the diaper region. In chronic cases, deeper follicular papules and pustules may be present (Fig. 17.15). Superficial infection responds well to topical antifungals, but when lesions are extensive or there is deeper follicular involvement, treatment with oral antifungals such as griseofulvin, fluconazole, or terbinafine may be required; experience with the use of terbinafine in neonates and very young infants is rather limited.



Figure 17.15 Diaper dermatophytosis due to *Trichophyton mentagrophytes*.

HERPES SIMPLEX INFECTION

Primary herpes infection (see Chapter 13) presents with painful vesicles, clustered on an erythematous base, 2–8 days after contact with an infected individual. Neonatal herpes may present in the diaper region following breech delivery of an infant whose mother has genital HSV. The diagnosis of genital HSV in an older infant or child may raise the suspicion of sexual abuse, although innocent transmission from an infected caregiver or parent may occur. Materno-fetal transmission of HSV resulting in neonatal HSV infection is discussed in Chapter 13.

CONDYLOMA ACUMINATA AND MOLLUSCA CONTAGIOSA

Verrucae are caused by cutaneous infection with the human papilloma virus (HPV); the infection is very common in children, although rare in neonates and infants. There are in excess of 100 HPV subtypes, most of which produce self-limited infection; a few subtypes in the genital area lead to malignancies. When verrucae affect the genital area they are known as condyloma acuminata. At least 30–40 subtypes are implicated in causing condyloma acuminata (see Chapter 13).⁷⁸ Acquisition in infancy is usually through maternal transmission. The incubation period is unknown and may be anywhere from 1 to more than 24 months. They can occur on any part of the perineum, including the vaginal area and around and extending into the anus. Lesions appear as asymptomatic, flesh-colored papules that may coalesce to form plaques. They have a characteristic verrucous, velvety surface (Fig. 17.16A,B,C).

Although it is well recognized that condyloma may be the result of child abuse, most cases in young infants are either vertically acquired or from unknown sources.⁷⁹ The exact percentage of cases acquired from sexual abuse in young infants is unknown and probably quite low, yet it is important to consider the possibility of abuse in all cases of genital HPV infection. There is a high rate of spontaneous resolution. Treatment regimens include imiquimod, podophyllin, and surgical removal (see Chapter 13).

Molluscum contagiosum (MC) is a poxviral infection of the skin characterized by discrete single or multiple, pink or flesh-colored, umbilicated papules.⁸⁰ There are four subtypes that are not area-specific. It is rarely seen in the neonatal period, but increases in incidence in early childhood; 80% of patients are



Figure 17.16 (A) A toddler with perianal condylomata.



Figure 17.16 (B,C) Perianal warts on two toddlers, secondary to child sexual abuse.



Figure 17.17 Molluscum contagiosum of diaper region.

under 8 years of age.⁸¹ The lesions are thought to be spread by autoinoculation; they tend to cluster in creases such as the axillae, the antecubital and popliteal fossae, and the diaper area (Fig. 17.17). The latter often raises the specter of child abuse, but supportive evidence is usually lacking and genital involvement is common.⁸¹ The disease is self-limited and often resolves with severe inflammation. Treatment includes curettage with topical anesthetics, liquid nitrogen (not an option in infants or young children), cantharidin and podophyllin.

COXSACKIE VIRAL EXANTHEM (HAND, FOOT, AND 'BUTT' EXANTHEM)

Hand, foot, and mouth disease is caused by various serotypes of coxsackie virus (CV), including A16, A5, A6, A9, A10, B1, and B3 (see Chapter 13). Infection with enterovirus 71 may cause a similar clinical presentation. The disease tends to be more severe in children under 5 years of age. Lesions consist of small red macules that rapidly evolve into ovoid vesicles. In the perineum, vesicles are rarely seen (Fig. 17.18A,B,C)⁸² except in patients infected with CVA6. Of affected children, 31% will have lesions in the buttocks or perineum, particularly those who are still wearing diapers (see Chapter 13).⁸³ In March 2012, the Centers for Disease Control reported outbreaks of CVA6 in several states.⁸⁴ Skin manifestations of this new strain include larger vesicles with widespread skin involvement and a predilection for active sites of dermatitis in atopic patients (Fig. 17.18A,B). Nail shedding occurs following recovery.

Nutritional and metabolic disorders

ZINC DEFICIENCY

Zinc is an essential mineral element that is necessary for the normal function of humans (see Chapter 18). An acute deficiency of zinc, through various mechanisms, is associated with a specific clinical picture in the skin. The dermatitis affects the periorificial areas of the face, the diaper area, and acral sites. Acrodermatitis enteropathica (AE) is a rare, recessively inherited disorder caused by a lack of zinc transfer from the small intestine.⁸⁵ A similar and much more frequent clinical picture is seen with other causes of low zinc levels, such as in breast-fed premature babies whose need for zinc outstrips the supply available in breast-milk. In rare cases, a similar etiology can



Figure 17.18 Hand, foot, and mouth disease. (A) Papules, vesicles and erosions on the buttocks in addition to the hands, feet, and perioral area.

occur in term infants whose mothers' breast-milk is deficient in zinc.⁸⁵ Zinc deficiency can also occur in malabsorption states, particularly when associated with cystic fibrosis (see below). Previously, zinc deficiency was reported in patients on parenteral alimentation, but it is rarely if ever seen now, as zinc is routinely added to the feeds. A picture resembling zinc deficiency may also be seen with other metabolic diseases, such as methylmalonic acid deficiency, biotin deficiency, essential fatty acid deficiency, and vitamin A acid deficiency.

Clinical presentation

The typical presentation is in a neonate or infant who develops a crusted, scaling, erythematous dermatitis around the face and in the diaper area (Fig. 17.19A,B). Lesions on the face assume a characteristic horseshoe appearance around the mouth. The periorbital area may also be involved. In the diaper area, lesions often affect the area around the anal cleft, with sharply demarcated erythema, superficial scale, and crusting at the periphery. Paronychia with candidal infection, maceration, and dermatitis are seen in the acral areas of the fingers and toes. Bullous lesions are rarely present on acral skin.

Extracutaneous manifestations

It is common to have marked irritability, diarrhea, sparse hair or alopecia, and recurrent infections, particularly with *Candida albicans*, but these may be absent early in the course of the disease, skin manifestations being the only finding. Nails may be dystrophic.

Etiology and pathogenesis

The etiology of AE is thought to be an abnormality in the region of chromosome 8q24.3 affecting the zinc transporter system at the level of the small intestine.⁸⁶ Zinc is a cofactor in many enzymatic responses, hence the heterogeneity of the clinical signs in the disease. The serum zinc level is low; blood should be collected in a plastic container to avoid erroneously high laboratory levels. Alkaline phosphatase levels may also be low, as zinc is a cofactor in this enzyme.

Prognosis and treatment

Oral zinc supplementation, given as zinc sulfate (3–5 mg/kg per day) or as zinc gluconate (which is better tolerated but more



Figure 17.18 (B) Coxsackie virus A6 infection with papules and vesicles in the diaper area, as well as on the extremities and face. (C) Severe coxsackie virus infection with dried vesicles, erosions and desquamation in the diaper area.



Figure 17.19 Zinc deficiency. (A) Periorificial eruption. (B) Diaper rash. The skin findings are typical of zinc deficiency, in this case caused by low levels of zinc in breast-milk.

expensive), results in the rapid reversal of the eruption and associated symptoms. Irritability is the first symptom to disappear. Patients with the genetic form of AE require treatment for life. Those infants with zinc deficiency due to a lack in breast-milk require zinc supplementation if breast-feeding is continued, but once formula or solid food is started the supplemental zinc is no longer needed.⁸⁷

DISORDERS THAT RESEMBLE ACRODERMATITIS ENTEROPATHICA

Biotin deficiency and certain organic acidurias⁸⁸ (see [Chapter 18](#)) may present with dermatitis of periorificial regions, including the diaper area, often in association with alopecia and changes in hair texture. The specific entities reported include deficiency of vitamin B₁₂ or isoleucine from restrictive diets or methylmalonic acidemia, propionic acidemia, glutaric aciduria (type 1),⁸⁹ maple syrup urine disease,⁹⁰ ornithine transcarbamylase deficiency,⁹¹ and citrullinemia.⁹² Cystic fibrosis may present in infancy with failure to thrive and an AE-like eruption.⁹³ Edema is usually severe in cystic fibrosis because of marked hypoalbuminemia and the characteristic mucosal and paronychia lesions of AE are usually absent.

Biotin deficiency may be induced by a diet high in raw egg white, which contains avidin, preventing the absorption of biotin. It has also been reported during prolonged parenteral nutrition containing inadequate replacement of biotin.

Several autosomal recessive disorders may present with AE-like eruptions because they require biotin as a cofactor, including methylmalonic acidemia, multiple carboxylase deficiency, and holocarboxylase deficiency.⁹⁴ Children undergoing long-term treatment with valproic acid for seizure disorders may have low biotin levels.⁹⁵

Miscellaneous

LANGERHANS' CELL HISTIOCYTOSIS

Langerhans' cell histiocytosis (LCH; see also [Chapter 26](#)) is a disease of unknown origin that is caused by an accumulation of bone marrow-derived cells that originate from the granulocyte series. Cells divide into the macrophage and dendritic cell series. LCH is a dendritic cell disorder and is the only histiocytic disease to affect neonates. The cells in this group of histiocytosis are all S100 and CD1a positive and have Birbeck granules on electron microscopy. The diaper area is often involved.

Clinical presentation

LCH affects 2.6 children per million child-years,⁹⁶ with boys slightly more affected than girls. Spontaneous regression often occurs in limited forms, so the incidence may be higher than recorded. The age group most often affected is from 1 to 4 years, but the disease may occur at birth and can affect any age. After bones, the skin, including the gums, teeth, and nails, is most commonly affected (40%).⁹⁷ Skin lesions may be single, few in number, or disseminated, and are the presenting sign in 50% of cases.⁹⁸ LCH in the newborn may involve the skin alone – congenital self-healing histiocytosis (Hashimoto–Pritzker disease), in which the majority of cases have nonspecific skin findings and are usually undiagnosed for a few months.⁹⁹ The most common sites affected in skin LCH are the trunk, scalp, behind the ears, the diaper area, and the skin folds. Lesions are protean in their presentation: papules, nodules, vesicles, erosions, ulcerations, petechiae and purpura, scale and crusting can all be present either alone or together ([Fig. 17.20A](#)). The color varies from erythematous to yellow or brown. Lesions in the diaper area are erythematous with peripheral petechiae. Ulcerations or atrophy involving the inguinal creases may be present ([Fig. 17.20B](#)).

Extracutaneous findings

Any organ may be affected in LCH, but it is unusual in the kidneys and gonads. In children under 2 with LCH, the disease is frequently disseminated (Letterer–Siwe disease), with skin and other organ involvement. The most common organ of involvement is bone (74%), followed by the skin (40%), lymph nodes (14%), and all other organs (<10%).⁹⁹

Etiology and pathogenesis

The precise etiology is unknown. Genetic factors have been implicated, as the disease is more common in monozygotic twins and in families. HLA studies have varied, but immune factors are thought to play a role. The theory of a reactive process invokes environmental factors, including malignancy.

Differential diagnosis

Owing to the diversity of the symptoms and signs, it is easy to miss the diagnosis. Conditions such as neuroblastoma, congenital leukemia, mastocytosis, and hemangiomas all present with

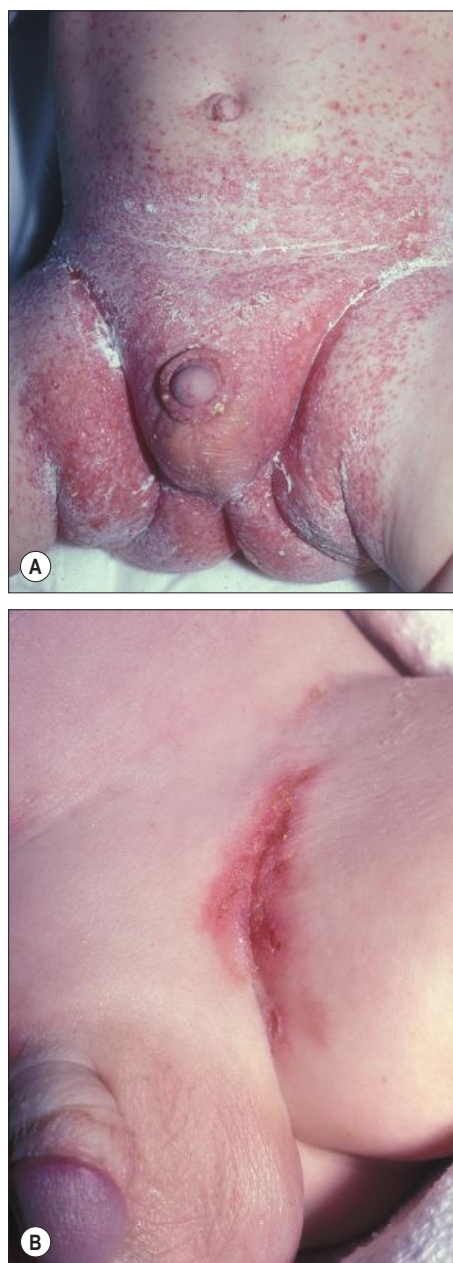


Figure 17.20 Langerhans' cell histiocytosis (LCH). (A) Extensive eruption resembles severe *Candida* infection, but purpuric papules near the umbilicus are typical of LCH. (B) LCH with ulceration in the inguinal crease.

nodular lesions. Pustular lesions such as erythema toxicum, neonatal pustular melanosis, and acropustulosis of infancy can all mimic LCH. The dermatitic variant is easily confused with ISD. Petechiae are a helpful sign of differentiation. Any patient resistant to standard treatment for ISD should be evaluated for LCH; both conditions affect the scalp and diaper area, and both have erythema and scaling. There is more crusting in LCH, and the presence of petechiae is a valuable distinguishing sign.

Prognosis and treatment

The diagnosis should be established based on biopsy and skin markers CD1a and S100 staining. The prognosis is not affected



Figure 17.21 Perianal pyramidal protrusion.

by the clinical appearance or the histology. In single-system skin disease, or where few skin lesions are present, it is important to monitor carefully for signs of other organ involvement and the appearance of diabetes insipidus. The prognosis in this group is good.⁹⁹ In the multinodular group of LCH called Hand–Schüller–Christian disease, the lesions are chronic and there may be an association with diabetes insipidus.¹⁰⁰ The multinodular groups have a better prognosis than the disseminated Letterer–Siwe disease, where the mortality rate under the age of 2 years is 50%.¹⁰¹ There are no good data on the definitive treatment of skin LCH. Treatment is geared toward the well-being of the patient, the number of organs involved, and the desire to minimize late effects. LCH involving multiple organs requires treatment (see [Chapter 28](#)).¹⁰²

INFANTILE PERIANAL PYRAMIDAL PROTRUSION

First described in 1996,¹⁰³ this entity consists of a protrusion around the anus that is often related to diarrhea, chronic constipation, or less commonly lichen sclerosis.¹⁰⁴ It has also been described in the literature as tags or skin folds.¹⁰⁵ The terminology has now been simplified to infantile perineal protrusion (IPP).¹⁰⁶

Cutaneous findings

IPP is fairly common, affecting up to 11% of prepubertal girls.¹⁰⁵ It has been reported in families,¹⁰⁴ and is almost exclusively seen in females.¹⁰⁵ The age range is usually between 1 and 30 months, but it has been reported at birth.¹⁰⁵ Parents, when prompted, will often give a history of chronic constipation or diarrhea as the initial event, prior to the appearance of IPP. The lesion may be asymptomatic or there may be pain on defecation; it is sometimes associated with fissuring. IPP usually appears on the perianal mucous membrane in the midline just anterior to the anal opening; it may less commonly be seen on the posterior aspect of the anus.¹⁰⁷ It is a pyramidal soft tissue protrusion with a tongue-like lip ([Fig. 17.21](#)).¹⁰⁴ The surface is smooth. The pathology is unremarkable, those having lichen sclerosis changes showing evidence of the disease on biopsy.¹⁰⁶

Extracutaneous findings

There may be a history of diarrhea or constipation from various causes.

Etiology and pathogenesis

The cause is unclear. IPP may be familial, functional (diarrhea or constipation), and lichen sclerosus-associated.¹⁰⁸ Neither weakness of the median raphe of the perineum, nor perineal constitutional weakness have been proven to be associated with IPP.

Differential diagnosis

Other conditions affecting the anal area should be considered. These include hemorrhoids, skin tags, condyloma acuminata, tag associated with anal fissure, inflammatory bowel disease, rectal prolapse, perineal midline malformation, and infantile hemangiomas.¹⁰⁴

Prognosis and treatment

Many cases resolve completely, and persistence is less common.¹⁰⁷ Attending to either constipation, diarrhea or fissuring may be helpful in accelerating the resolution. If lichen sclerosus is present, then treatment with high-potency corticosteroids is useful. Observation, with petrolatum applied to the area is usually all that is needed.

NASCENT HEMANGIOMA

Infantile hemangiomas (see Chapter 21) located in the perineum frequently become ulcerated, and this may actually be the presenting finding in a minority of patients. In these cases, an infant will be born with or develop an ulceration in the perineum in the first few days of life prior to a hemangioma being evident. Close inspection will often reveal telangiectasia or vascular papules at the margin of the ulceration, or occasionally in the surrounding skin (Fig. 17.22A). Days to several weeks later, a superficial plaque-type or minimal/arrested growth hemangioma will develop in the region (Fig. 17.22B). Undiagnosed ulceration due to nascent hemangioma may be misdiagnosed as a rapidly expanding bacterial or viral infection, thermal burn, or child abuse.¹⁰⁹ The etiology of ulceration in nascent hemangiomas is unclear, but may be related to rapid apoptosis of endothelial cells in a portion of the evolving hemangioma.



Figure 17.22 (A) A 1-month-old infant with a nascent hemangioma presenting with perianal ulceration.

LICHEN SCLEROSUS (LS)

This disease of unknown origin affects the genital area of female children with a well-recognized clinical and histologic picture. The two main ages of presentation are in prepubertal and postmenopausal females. The male equivalent of LS is called balanitis xerotica obliterans (BXO). Autoimmune, genetic and other etiologies have been implicated but not proved.¹¹⁰ Cases during infancy are uncommon, but the presence of histologic changes of LS in boys with congenital phimosis and a documented association with perineal pyramidal protrusion suggests that onset may occur quite early in infancy.¹¹¹ The mean age of presentation is 5 years but it may occur anywhere from 1–12 years. The eruption may be asymptomatic, but usually presents with pruritus in the genital area, and constipation. Pain, dysuria and bleeding may also occur in girls and phimosis in boys with BXO.¹¹²

Constipation is related to fissuring of the perianal skin, pain on defecation and subsequent atony of the bowel associated with holding the stool. The classic clinical picture is of a white, glistening, atrophic vulvar area, often with accentuation of the veins and wrinkling of the skin (Fig. 17.23A). The lesions may extend onto the anal area in a figure-of-eight distribution (Fig. 17.23B). Hemorrhagic areas and petechiae may be seen (Fig. 17.23C). It is important to differentiate LS from child abuse and herpes simplex infection. If left untreated, adhesions, flattening of the clitoris, and narrowing of the vaginal opening may occur. Response to potent topical steroids is excellent, but recurrence may occur.¹¹³ In boys, circumcision may be necessary to relieve the balanitis.

PYODERMA GANGRENOSUM

Pyoderma gangrenosum (see Chapter 10) presents as papules that develop into pustules and then rapidly expand into painful deep ulcerations surrounded by a violaceous border. Pathergy often occurs. Although rare in infants, a case has been reported in a 3-week-old infant presenting with perineal lesions.¹¹⁴ Crohn disease should be considered when lesions of pyoderma gangrenosum develop in the perianal region, particularly with



Figure 17.23 (A) Lichen sclerosus in a toddler.



Figure 17.22 (B) Nascent hemangioma with ulceration in patient with LUMBAR association (lower body hemangioma and other cutaneous defects, urogenital anomalies, ulceration, myelopathy, bony deformities, anorectal malformations, arterial anomalies, and renal anomalies).

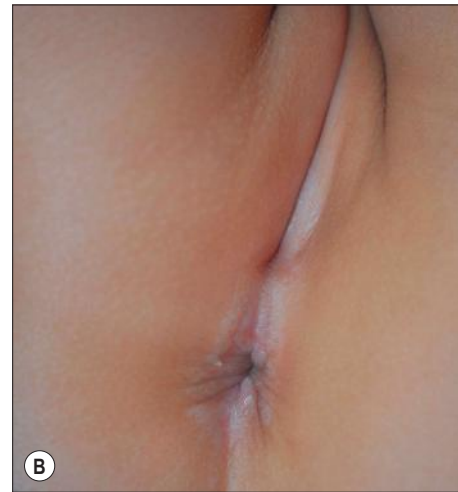


Figure 17.23 (B) Perianal lichen sclerosus in a toddler. (C) Lichen sclerosus in a young infant; in addition to hypopigmentation and atrophy, hemorrhage is a relatively common finding.

features of skin tags, perianal fissuring, and a history of diarrhea or constipation.¹¹⁵

CHRONIC BULLOUS DISEASE OF CHILDHOOD (CBDC)

CBDC or linear IgA disease is an acquired blistering disorder that involves the skin and mucous membranes. The etiology of CBDC is unknown (see [Chapters 10 and 11](#)); studies implicating infectious, drug, or autoimmune diseases have been inconclusive. Commonly, preschool children present with fever or other constitutional findings, followed by large tense bullae that are annular or polycyclic. The lesions are described as resembling a string of pearls. The underlying skin is normal. The diaper area is characteristically involved, with other common areas that include the face, trunk, and legs, although any site can be affected ([Fig. 17.24](#)).¹¹⁶ Although not recognized initially, mucous membranes, particularly the oral mucosa, are frequently involved. Erosions and occasional intact bullae are seen. Conjunctival erosions are not uncommon. The bullae are subepidermal and filled with neutrophils. Direct immunofluorescence demonstrates a linear band of IgA staining at the dermo-epidermal junction. The prognosis for remission without treatment is between 3 and 5 years, although the disease

may persist into adult life. Treatments include dapsone, sulfapyridine, and prednisone, with good results. When the lesions heal, there are no recurrences.¹¹⁷

BULLOUS PEMPHIGOID (BP)

A rare disease in childhood, BP is an acquired blistering disorder that overlaps with CBDC (see [Chapters 10 and 11](#)). It has been recorded in infants as young as 2–3 months of age. In those under 1 year, it is more common in females. Patients with BP typically present with tense bullae on a normal or erythematous base, and urticarial lesions. Common areas of involvement include the face, and the diaper area but in infants bullae are particularly common on the hands and feet. A variant of BP confined to the vulval area is known as localized vulval pemphigoid and this is more common in older females. Typically, BP antigens are designated BP 230 and 180. Immunofluorescence demonstrates IgG and C3 at the dermo-epidermal junction and histology shows a subepidermal bulla with eosinophils.¹¹⁸ The prognosis is good, with remission within 1 year. Systemic or topical steroids in addition to other systemic agents have been used with good effect.¹¹⁸

KAWASAKI SYNDROME

Kawasaki syndrome (see [Chapter 20](#)) is a well-characterized febrile illness affecting many organs including aneurysms of the cardiac vessels with prominent cutaneous manifestations.¹¹⁹ Approximately two-thirds of affected infants may have prominent erythema and early desquamation in the perineal area ([Fig. 17.25](#)). This finding can be an important clue to diagnosis, as it often occurs early in the disease, before the presence of other diagnostic findings such as desquamation of the fingers and toes. The inguinal creases are often the most prominent area of involvement, but the entire perineal area may be involved. The initial bright-red erythema may persist or fade, resolving with prominent desquamation. Small sterile pustules are sometimes present.^{120,121}

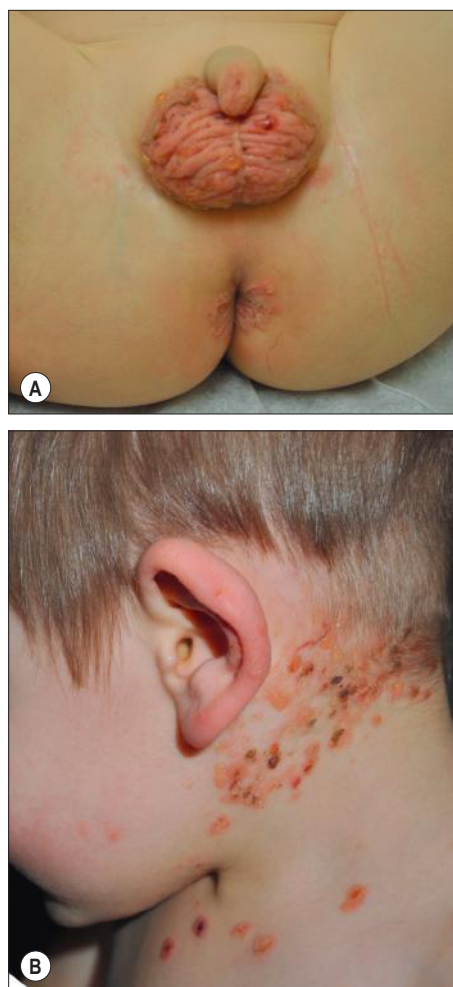


Figure 17.24 (A,B) Chronic bullous disease of childhood (linear IgA disease). Scrotal and neck lesions in a 2-year-old child.



Figure 17.25 Perineal erythema and scale in a young infant with Kawasaki syndrome.

CLEAR-CELL PAPULOSIS

Clear-cell papulosis is a distinctive condition presenting with multiple, hypopigmented, flat-topped papules in the pubic region and on the abdomen.¹²² Several cases have been described with onset as early as 3 months of age. A few cases have been familial. The lesions are generally asymptomatic. The distribution pattern of these papules follows the milk lines. Histopathologic examination shows large clear cells within the lower epidermis, which stain positively with periodic acid-Schiff. Interestingly, these cells are now understood to represent so-called 'Toker cells', the same cells which are found in

cutaneous Paget disease. There is no evidence that this condition eventuates to cutaneous Paget disease, however. The differential diagnosis includes idiopathic guttate hypomelanosis, small scars, e.g., chickenpox scars, tinea versicolor, anetoderma, evolving vitiligo, and flat warts. Diagnosis is confirmed with skin biopsy.

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Figures 2B, 3B, 9D, 12C, 14B, 16B, C, 18B, C, 22B and 23B, C are available online at [ExpertConsult.com](#) 

KEY REFERENCES

7. Visscher MO, Chatterjee R, Muinson KA, et al. Development of diaper rash in the newborn. *Pediatr Dermatol* 2000;17:52–7.
14. Tokar B, Urer S. Factors determining the severity of perianal dermatitis after enterostoma closure of pediatric patients. *Int J Dermatol* 2005;44:168–9.
40. Morris A, Rogers M, Fischer G, et al. Childhood psoriasis: a clinical review of 1262 cases. *Pediatr Dermatol* 2001;18:188–98.
45. Smith WJ, Jacob SE. The role of allergic contact dermatitis in diaper dermatitis. *Pediatr Dermatol* 2009;26(3):369–70.
58. Hoppe JE. Treatment of oropharyngeal candidiasis and candidal diaper dermatitis in neonates and infants: review and reappraisal. *Pediatr Infect Dis J* 1997;16:885–94.
70. Heath C, Desai N, Silverberg N. Recent microbiological shifts in perianal bacterial dermatitis: *Staphylococcus aureus* predominance. *Pediatr Dermatol* 2009;26(6):696–700.
78. Sinclair KA, Woods CR, Kirse DJ, et al. Anogenital and respiratory tract human papillomavirus infections among children: age, gender, and potential transmission through sexual abuse. *Pediatrics* 2005;116:815–25.
81. Dohil MA, Lin P, Lee J, et al. The epidemiology of molluscum contagiosum in children. *J Am Acad Dermatol* 2006;54:47–54.
84. Centers for Disease Control and Prevention (CDC). Notes from the field: severe hand, foot, and mouth disease associated with coxsackievirus A6 – Alabama, Connecticut, California, and Nevada, November 2011–February 2012. *MMWR Morb Mortal Wkly Rep* 2012;61(12):213–14.
110. Smith SD, Fischer G. Paediatric vulval lichen sclerosis. *Australas J Dermatol* 2009;50(4):243–8.

REFERENCES

- Lund CH, Kuller J, Lane AT, et al. Neonatal skin care: clinical outcomes of the AWHONN/ NANN evidence-based clinical practice guideline. *J Obstet Gynecol Neonat Nurs* 2001;30: 41–51.
- Jacquet L. Traité des maladies de l'enfance. In: Grancher J, Comby J, Marfan AB, editors. Traité des maladies de l'enfance. Paris: Masson & Co; 1905. p. 714.
- Zahorsky J. The ammoniacal diaper in infants and young children. *Am J Dis Child* 1915; 10:436.
- Jordon WE, Lawson KD, Berg RW, et al. Diaper dermatitis: frequency and severity among a general infant population. *Pediatr Dermatol* 1986;3:198–207.
- Ward DB, Fleischer AB Jr, Feldman SR, et al. Characterization of diaper dermatitis in the United States. *Arch Pediatr Adolesc Med* 2000; 154:943–6.
- Lane AT, Rehder PA, Helm K. Evaluations of diapers containing absorbent gelling material with conventional disposable diapers in newborn infants. *Am J Dis Child* 1990;144: 315–18.
- Visscher MO, Chatterjee R, Muinson KA, et al. Development of diaper rash in the newborn. *Pediatr Dermatol* 2000;17:52–7.
- Visscher MO, Chatterjee R, Munson KA, et al. Changes in diapered and non-diapered skin over the first month of life. *Pediatr Dermatol* 2000;17:45–51.
- Berg RW, Milligan MC, Sarbaugh FC. Association of skin wetness and pH with diaper dermatitis. *Pediatr Dermatol* 1994;11:18–20.
- Warner RR, Stone KJ, Boissy YL. Hydration disrupts stratum corneum ultrastructure. *J Invest Dermatol* 2003;120:275–84.
- Berg RW, Buckingham KW, Stewart RL. Etiologic factors in diaper dermatitis: the role of urine. *Pediatr Dermatol* 1986;3:102–6.
- Fluhr JW, Elias PM. Stratum corneum pH: formation and function of the 'acid mantle.' *Exog Dermatol* 2002;1:163–75.
- Heimall LH, Storey B, Stellar JJ et al. Beginning at the bottom: evidence-based care of diaper dermatitis. *MCN Am J Matern Child Nurs* 2012;37(1):10–16.
- Tokar B, Urer S. Factors determining the severity of perianal dermatitis after enterostoma closure of pediatric patients. *Int J Dermatol* 2005;44:168–9.
- Berger S, Ruefener J, Klimek P et al. Effects of potato-derived protease inhibitors on perianal dermatitis after colon resection for long segment Hirschsprung's disease. *World J Pediatr* 2012;8(2):173–6.
- Robson KJ, Maughan JA, Purcell SD, et al. Erosive papulonodular dermatosis associated with topical benzocaine: a report of two cases and evidence that granuloma gluteale, pseudoverrucous papules and Jacquet's erosive dermatitis area a disease spectrum. *J Am Acad Dermatol* 2006;55(Suppl. 5):S74–80.
- Goldberg NS, Esterly NB, Rothman KF, et al. Perianal pseudoverrucous papules and nodules in children. *Arch Dermatol* 1992;128: 240–2.
- Rodriguez-Poblador J, Gonzalez-Castro U, Herranz-Martinez S, et al. Jacquet erosive diaper dermatitis after surgery for Hirschsprung disease. *Pediatr Dermatol* 1998;15:46–7.
- Tappeiner J, Pfleger L. Granuloma gluteale infantum. *Hautarzt* 1971;22:383–8.
- Delacretaz J, Grigoriu D, De Crousaz H, et al. Candidose nodulaire de la région inguinogénitale et des fesses. *Dermatologica* 1972;144:144.
- Ortonne J, Perrot H, Thivolet J. Granuloma gluteale infantile (GGI): Etude ultrastructurale. *Ann Dermatol Venerol (Paris)* 1980; 107:631–4.
- Dytoc M, Fiorillo L, Liao J, et al. Granuloma gluteale adutorum associated with use of topical benzocaine preparations: Case report and literature review. *J Cutan Med Surg* 2002;6:221–5.
- Spiller HA, Winter MA, Weber JA, et al. Skin breakdown and blisters from senna-containing laxatives in young children. *Ann Pharmacother* 2003;37:636–9.
- Smith WA, Taintor AR, Kos L. et al. Senna-containing laxative inducing blistering dermatitis in toddlers. *Arch Dermatol* 2012;148(3): 402–4.
- Chang MW, Kaufmann JM, Orlow SJ, et al. Infantile granular parakeratosis: Recognition of two clinical patterns. *J Am Acad Dermatol* 2004;50: S93–6.
- Patrizi A, Neri I, Misciali C, et al. Granular parakeratosis: four pediatric cases. *Br J Dermatol* 2002;147:1003–6.
- Metze D, Rutten A. Granular parakeratosis – a unique acquired disorder of keratinization. *J Cutan Pathol* 1999;26:339–52.
- Samrao A, Reis M, Neidt G et al. Granular parakeratosis: response to calcipotriene and brief review of therapeutic options. *Skinmed* 2010;8(6):357–9.
- Unna PG. Seborrheic eczema. *J Cutan Dis* 1887;5:499.
- Williams JV, Eichenfield LF, Burke BL, et al. Prevalence of scalp scaling in prepubertal children. *Pediatrics* 2005;115:e1–6.
- Gupta AK, Bluhm R. Seborrheic dermatitis. *J Eur Acad Dermatol Venerol* 2004;18: 13–26.
- Wananukul S, Chindamporn A, Yumyoun P, et al. Malassezia furfur in infantile seborrheic dermatitis. *Asia Pacific J Allergy Immunol* 2005;23:101–5.
- Mimouni K, Mukamel M, Zaheria A, et al. Prognosis of infantile seborrheic dermatitis. *J Pediatr* 1995;127:744–6.
- Erlichman M, Goldstein R, Levi E, et al. Infantile flexural seborrheic dermatitis. Neither biotin nor essential fatty acid deficiency. *Arch Dis Childhood* 1981;56:560–2.
- Wannanukul S, Chiabunkana J. Comparative study of 2% ketoconazole cream and 1% hydrocortisone cream in the treatment of infantile seborrheic dermatitis. *J Med Assoc Thai* 2004;87: S68–71.
- Cohen S. Should we treat infantile seborrheic dermatitis with topical antifungals or topical steroids? *Arch Dis Childhood* 2000;89: 288–9.
- Farber EA, Jacobs AH. Infantile psoriasis. *Am J Dis Child* 1977;131:1266.
- Farber EM, Nall L. Epidemiology: natural history and genetics. In: Roenigk HH Jr, Maibach HI, editors. *Psoriasis*. 3rd ed. New York: Marcel Dekker; 1998. p. 107–58.
- Farber EM. Juvenile psoriasis. Early interventions can reduce risk for problems later. *Postgrad Med* 1998;103:89–100.
- Morris A, Rogers M, Fischer G, et al. Childhood psoriasis: a clinical review of 1262 cases. *Pediatr Dermatol* 2001;18:188–98.
- Fergusson AG, Fraser ND, Grant PW. Napkin dermatitis with psoriasiform 'id.' *Br J Dermatol* 1966;78:289–96.
- Rattet JP, Headley JL, Barr RJ. Diaper dermatitis with psoriasiform ID eruption. *Int J Dermatol* 1981;20:122–5.
- Nevill EA, Finn OA. Psoriasiform napkin dermatitis: a follow-up study. *Br J Dermatol* 1975; 92:279.
- Friedlander SF. Contact dermatitis. *Pediatr Rev* 1998;19:166–71.
- Smith WJ, Jacob SE. The role of allergic contact dermatitis in diaper dermatitis. *Pediatr Dermatol* 2009;26(3):369–70.
- Weston WL, Weston JA. Allergic contact dermatitis in children. *Am J Dis Child* 1984;138: 932–6.
- Bruckner AL, Weston WL, Morelli JG. Does sensitization to contact allergens begin in infancy? *Pediatrics* 1986;78:1070–4.
- Barros MA, Baptista A, Correia M, et al. Patch testing in children: a study of 562 school children. *Contact Dermatitis* 1991;25(3):156–9.
- Roul S, Ducombs G, Leaute-Labreze C, et al. 'Lucky Luke' contact dermatitis due to rubber components of diapers. *Contact Dermatitis* 1998;38(6):363–4.
- Onken AT, Baumstark J, Belloni B et al. Atypical diaper dermatitis: contact allergy to mercapto compounds. *Pediatr Dermatol* 2011; 28(6):739–41.
- Alberta L, Sweeney SM, Wiss K. Diaper dye dermatitis. *Pediatrics* 2005;116:e450–2.
- Ruiz-Diez B, Martinez V. Molecular tracking of *Candida albicans* in a neonatal intensive care unit: long-term colonizations versus catheter-related infections. *J Clin Microbiol* 1997;35: 3032–6.
- Bound JP. Thrush napkin rashes. *BMJ* 1956; 1:782.
- Beare JM, Cheeseman EA, MacKenzie DWR. The association between *Candida albicans* and lesions of seborrheic eczema. *Br J Dermatol* 1968;80:675–81.
- Leyden J. The role of microorganisms in diaper dermatitis. *Arch Dermatol* 1978;114:56–9.
- Rebora A, Leyden J. Napkin (diaper) dermatitis and gastrointestinal carriage of *Candida albicans*. *Br J Dermatol* 1981;105:551–5.
- Tieu KD, Satter EK, Zaleski L, et al. Congenital cutaneous candidiasis in two full-term infants. *Pediatr Dermatol* 2012;29(4):507–10.
- Hoppe JE. Treatment of oropharyngeal candidiasis and candidal diaper dermatitis in neonates and infants: review and reappraisal. *Pediatr Infect Dis J* 1997;16:885–94.
- Spraker MK, Gisoldi EM, Siegfried EC, et al. Topical miconazole nitrate ointment in the treatment of diaper dermatitis complicated by candidiasis. *Cutis* 2006;77:113–20.
- Munz D, Powell KR, Pai CH. Treatment of candidal diaper dermatitis: a double-blind placebo-controlled comparison of topical nystatin with topical plus oral nystatin. *J Pediatr* 1982;101:1022–5.
- Darmstadt G, Lane AT, Impetigo. An overview. *Pediatr Dermatol* 1994;11:293–303.
- Elias P, Fritsch P, Dahl MS. Staphylococcal toxic epidermal necrolysis. Pathogenesis and studies on the subcellular site of action of exfoliating. *J Invest Dermatol* 1975;65:501–12.
- Yamasaki O, Yamaguchi T, Sugai M, et al. Clinical manifestations of staphylococcal scalded skin syndrome depend on T serotypes

- of exfoliatin organisms. *J Clin Microbiol* 2005; 43:1890–3.
64. Amagai M, Yamaguchi T, Hanakawa Y, et al. Staphylococcal exfoliative toxin B specifically cleaves desmoglein 1. *J Invest Dermatol* 2002; 118:845–50.
 65. Drucker C. Update on topical antibiotics in dermatology. *Dermatol Therapy* 2012;25: 6–11.
 66. Amren DP, Anderson AS, Wannamaker LW. Perianal cellulites associated with group A streptococci. *Am J Dis Child* 1966;112: 546–52.
 67. Krol AL. Perianal streptococcal dermatitis. *Pediatr Dermatol* 1990;7:97–100.
 68. Kolx NP, Comstock JA, Facklam RR. Streptococcal perianal disease in children. *Pediatrics* 1987;80:659–63.
 69. Honig P, Frieden I, Kim H, et al. Streptococcal intertrigo: an underrecognized condition in children. *Pediatrics* 2003;112:1427–9.
 70. Heath C, Desai N, Silverberg N. Recent microbiological shifts in perianal bacterial dermatitis: *Staphylococcus aureus* predominance. *Pediatr Dermatol* 2009;26(6):696–700.
 71. Mogilnicki NP, Schwartzman JD, Elliott JA. Perineal group A streptococcal disease in a pediatric practice. *Pediatrics* 2000;106:276–81.
 72. Gucular H, Ergun T, Demircay Z. Ecthyma gangrenosum. *Int J Dermatol* 1999;38:298–305.
 73. Taieb A, Boisseau AM, Sarlangue J, et al. Gangrenous ecthyma of the diaper area in infants. *Ann Pediatr (Paris)* 1992;39:443–6.
 74. Tutrone WD, Scheinfeld NS, Weinberg JM. Cutaneous anthrax: a concise review. *Cutis* 2002;69:27–33.
 75. Koo SH, Lee JH, Shin H, et al. Ecthyma gangrenosum in a previously healthy infant. *Arch Plast Surg* 2012;39(6):673–5.
 76. Parry EL, Foshee WS, Marks JG. Diaper dermatophytosis. *Am J Dis Child* 1982;136: 273–4.
 77. Baudraz-Rosselet F, Ruffieux PH, Mancarella A, et al. Diaper dermatitis due to *Trichophyton verrucosum*. *Pediatr Dermatol* 1993;10:368–9.
 78. Sinclair KA, Woods CR, Kirse DJ, et al. Anogenital and respiratory tract human papillomavirus infections among children: age, gender, and potential transmission through sexual abuse. *Pediatrics* 2005;116:815–25.
 79. Handley J, Hanks E, Armstrong K, et al. Common association of HPV2 in anogenital warts in prepubertal children. *Pediatr Dermatol* 1997;14:339–43.
 80. Gottlieb SL, Myskowski PL. Molluscum contagiosum. *Int J Dermatol* 1994;33:45.
 81. Dohil MA, Lin P, Lee J, et al. The epidemiology of molluscum contagiosum in children. *J Am Acad Dermatol* 2006;54:47–54.
 82. Slavin KA, Frieden IJ. Picture of the month: hand, foot and mouth disease. *Arch Pediatr Adolesc Med* 1998;152:505–6.
 83. Richardson HB Jr, Leibovitz A. Hand, foot, and mouth disease in children. *J Pediatr* 1965; 67:6–12.
 84. Centers for Disease Control and Prevention (CDC). Notes from the field: severe hand, foot, and mouth disease associated with coxsackievirus A6 – Alabama, Connecticut, California, and Nevada, November 2011–February 2012. *MMWR Morb Mortal Wkly Rep* 2012;61(12):213–14.
 85. Aggett PJ, Harries JT. The current status of zinc in health and disease states. *Arch Dis Child* 1979;54:909–17.
 86. Wang K, Pugh EW, Griffen S, et al. Homozygosity mapping places the acrodermatitis enteropathica gene on chromosome region 8q24.3. *Am J Hum Genet* 2001;68:1055–60 Epub 2001.
 87. Perafan-Riveros C, Sayago-Franca LF, Fortes-Alves AC, et al. Acrodermatitis enteropathica: Case report and review of the literature. *Pediatr Dermatol* 2002;19:426–31.
 88. De Raevae L, De Meirleir L, Ramet J, et al. Acrodermatitis enteropathica-like cutaneous lesions in organic aciduria. *J Pediatr* 1994;124: 416–20.
 89. Niyama S, Koelker S, Degen I, et al. Acrodermatitis academia secondary to malnutrition in glutaric aciduria type 1. *Eur J Dermatol* 2001; 11:244–6.
 90. Koch SE, Pachman S, Koch TK, et al. Dermatitis in treated maple syrup urine disease. *J Am Acad Dermatol* 1993;28:289–92.
 91. Lee JY, Chang SE, Suh CW, et al. A case of acrodermatitis enteropathica-like dermatosis caused by ornithine transcarbamylase deficiency. *J Am Acad Dermatol* 2002;46:965–7.
 92. Goldblum OM, Brusilow SW, Maldonado YA, et al. Neonatal citrullinemia associated with cutaneous manifestations and arginine deficiency. *J Am Acad Dermatol* 1986;14:321–6.
 93. Crone J, Huber WD, Eichler I, et al. Acrodermatitis enteropathica-like eruption as the presenting sign of cystic fibrosis. Case report and review of the literature. *Eur J Pediatr* 2002; 161:475–8.
 94. Seymons K, De Moor A, De Raevae H, et al. Dermatologic signs of biotin deficiency leading to the diagnosis of multiple carboxylase deficiency. *Pediatr Dermatol* 2004;21:231–5.
 95. Schulpis KH, Karikas GA, Tjamosanis J, et al. Low serum biotinidase activity in children with valproic acid monotherapy. *Epilepsia* 2001;42:1359–62.
 96. Alston RD, Tatevossian RG, McNally RJ, et al. Incidence and survival of childhood Langerhans cell histiocytosis in Northwest England from 1954 to 1998. *Pediatr Blood Cancer* 2007;48(5):555–60.
 97. The French Langerhans' Cell Histiocytosis Study Group. A multicenter retrospective survey of LCH: 348 cases observed between 1983–1993. *Arch Dis Child* 1996;75:17–24.
 98. Munn S, Chu AC. Langerhans' cell histiocytosis of the skin. *Hematol Oncol Clin North Am* 1998;12:269–86.
 99. Stein SL, Paller AS, Haut PR, et al. Langerhans' cell histiocytosis presenting in the neonatal period: a retrospective case series. *Arch Pediatr Adolesc Med* 2001;155:778–83.
 100. Yu RC, Chu AC. Lack of T-cell rearrangement in cells involved in Langerhans' cell histiocytosis. *Cancer* 1995;75:1162–6.
 101. Rivera-Luna R, Alter-Molchadsky N, Cardenas-Cardos R, et al. Langerhans' cell histiocytosis in children under 2 years of age. *Med Pediatr Oncol* 1996;26:70–4.
 102. Ladisch S, Gadner H. Treatment of Langerhans' cell histiocytosis: evolution and current approaches. *Br J Cancer* 1994;70: S41–6.
 103. Kayashima K, Kitoh M, Ono T. Infantile perianal pyramidal protrusion. *Arch Dermatol* 1996;132:1481–4.
 104. Amor Khachemoun CW, Kjetil KG, Ehram E. Infantile perineal protrusion. *J Am Acad Dermatol* 2006;54:1046–9.
 105. Cruces MJ, De La Torre C, Losada A, et al. Infantile pyramidal protrusion as a manifestation of lichen sclerosus et atrophicus. *Arch Dermatol* 1998;134:1118–20.
 106. Merigou D, Labreze C, Lamireau T, et al. Infantile perianal pyramidal protrusion: a marker of constipation. *Pediatr Dermatol* 1998;15: 143–4.
 107. Patrizi A, Baone B, Neri I, et al. Infantile perianal protrusion: 13 new cases. *Pediatr Dermatol* 2002;19:15–18.
 108. McCann J, Voris J, Simon M, et al. Infantile perineal findings in prepubertal children selected for nonabuse: a descriptive study. *Child Abuse Neglect* 1989;13:1799.
 109. Liang MG, Frieden IJ. Perineal and lip ulcerations as the presenting manifestations of hemangioma of infancy. *Pediatrics* 1997;99: 256–9.
 110. Smith SD, Fischer G. Paediatric vulval lichen sclerosus. *Australas J Dermatol* 2009;50(4): 243–8.
 111. Fischer G, Rogers M. Vulvar disease in children: a clinical audit of 130 cases. *Pediatr Dermatol* 2000;17:1–6.
 112. Maronn ML, Esterly NB. Constipation as a feature of anogenital lichen sclerosus in children. *Pediatrics* 2005;115:e230–2.
 113. Smith YR, Haefner HK. Vulval lichen sclerosus: Pathophysiology and treatment. *Am J Clin Dermatol* 2004;5:105–25.
 114. Graham JA, Hansen KK, Rabinowitz LG, et al. Pyoderma gangrenosum in infants and children. *Pediatr Dermatol* 1994;11:10–17.
 115. Dinulos JG, Darmstadt GL, Len MK, et al. Infantile Crohn disease presenting with diarrhea and pyoderma gangrenosum. *Pediatr Dermatol* 2006;23:43–8.
 116. Sansaricq F, Stein SL, Petronic-Rosic V. Auto-immune bullous diseases in childhood. *Clin Dermatol* 2012;30(1):114–27.
 117. Kanwar AJ, Sandhu K, Handa S. Chronic bullous disease of childhood in north India. *Pediatr Dermatol* 2004;21:610–12.
 118. Waisbourd-Zinman O, Ben-Amitai D, et al. Bullous pemphigoid in infancy: Clinical and epidemiologic characteristics. *J Am Acad Dermatol* 2008;58:41–8.
 119. Falcini F. Kawasaki disease. *Curr Opin Rheumatol* 2006;18:33–8.
 120. Friter BS, Lucky AW. The perineal eruption of Kawasaki syndrome. *Arch Dermatol* 1988;124: 1805–10.
 121. Krowchuk DP, Bass J, Elgart GW. Kawasaki disease with an exanthem limited to the diaper area. *Am J Dis Child* 1988;142:1136–7.
 122. Lee JY, Chao SC. Clear cell papulosis of the skin. *Br J Dermatol* 1998;138(4):678–83.

Erythrodermas, Immunodeficiency, and Metabolic Disorders

MOISE L. LEVY

Erythrodermas

The term 'erythroderma' is used in dermatology to describe a skin eruption characterized by diffuse erythema, usually in association with scaling. Infantile erythroderma is caused by or associated with a large number of disorders (Box 18.1). The differential diagnosis includes inflammatory, infectious, inherited, and immunologic diseases, many of which have a hereditary basis. Some of these diseases are potentially life-threatening, and erythroderma itself can cause serious medical complications, such as electrolyte imbalance, sepsis, and temperature instability resulting from heat loss. It is therefore important for the physician to accurately diagnose and treat the problem.

Inflammatory diseases

ATOPIC DERMATITIS

Severe generalized atopic dermatitis is unusual in neonates, though may often be seen in infancy. Because atopic dermatitis is such a common problem, it is the most common cause of acquired erythroderma in infants (see Chapter 15). Classic infantile atopic dermatitis involves the scalp, cheeks, and extensor surfaces of the extremities and may not appear until the infant is several months of age.¹ When the distribution is generalized and the onset is early, diagnosis can be more difficult.

The presence of pruritus, an almost invariable feature of this condition, is not always apparent in neonates and young infants. There is often a family history of atopy. Typically, the diaper region is spared, even in cases of widespread atopic dermatitis, as a result of the moist, occlusive environment of diapered skin. In contrast to infants with severe metabolic or immunologic disease, infants with atopic dermatitis usually grow normally and thrive, assuming the disease is recognized and treated promptly. Severe and long-standing disease, however, can be a cause of failure to thrive. Other clinical features such as repeated pneumonia, viral infections such as HSV or molluscum, and skeletal abnormalities may suggest the autosomal dominant hyper-IgE syndrome (HIES) or the autosomal recessive DOCK8 deficiency syndrome.^{2,3} Atopic dermatitis generally responds rapidly to appropriate therapy with topical anti-inflammatory agents and emollients. Skin biopsy in atopic dermatitis demonstrates acanthosis (thickening of the epidermis) and varying degrees of spongiosis (epidermal edema), as well as lymphohistiocytic inflammatory infiltrates, often with scattered eosinophils and plasma cells.⁴

SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a common problem during the neonatal period and is generally easily recognized (see also Chapter

15). Typically, there is scaling and erythema involving seborrheic areas such as the scalp and body folds. The yellow, greasy, scalp scale may encompass the entire forehead, including the eyebrows, and erythema and maceration can involve body folds such as the retroauricular areas, neck, axillae, and groin. Occasionally, a more diffuse pattern of seborrheic dermatitis can occur, which must be distinguished from atopic dermatitis, neonatal candidiasis, psoriasis, and other causes of infantile erythroderma (Box 18.1 and Fig. 18.1).

The distribution of the dermatitis is more helpful than any other criterion in differentiating between atopic and seborrheic dermatitis, but it can be difficult and sometimes impossible to differentiate the two conditions accurately early in their course. Although the scalp can be red and scaly in both conditions, seborrheic dermatitis tends to involve the groin and other body folds, which are generally spared in atopic dermatitis. As treatment for both conditions in infancy is similar, from a practical standpoint accurate differentiation can be an academic exercise. However, the course of this disease differs: seborrheic dermatitis usually resolves over several months, whereas atopic dermatitis often persists for several years. Skin biopsy findings in seborrheic dermatitis are similar to those in atopic dermatitis. There is mild acanthosis, spongiosis, and a mild lymphohistiocytic inflammatory infiltrate; parakeratotic scale may be present.

If clinical features suggest widespread seborrheic dermatitis in an infant who is otherwise well and thriving, and the skin readily clears after the application of low- to mid-potency topical corticosteroids without chronic rebound when therapy is tapered, the diagnosis of seborrheic dermatitis is probably accurate. Otherwise, alternative diagnoses should be considered. Severe seborrheic dermatitis in a child who is not thriving can suggest an immunodeficiency or Netherton syndrome.

PSORIASIS

Less than 1% of all cases of psoriasis are said to occur in children less than 1 year of age. Infantile psoriasis can be difficult to diagnose because of its clinical similarity to both seborrheic dermatitis and atopic dermatitis. Infantile psoriasis can look like that seen in older individuals, with discrete oval erythematous plaques with white scale involving the trunk, extremities, and face. Psoriatic plaques in infants may have less hyperkeratosis than usually seen in adults. Facial involvement is more common in the infant, and the scalp, palms, and soles may have diffuse erythema and scaling. A periumbilical distribution may be helpful in distinguishing psoriasis from either seborrheic or atopic dermatitis. In contrast to atopic dermatitis, psoriasis in young infants often involves the diaper area because it develops in areas of injured skin (the Koebner phenomenon), e.g. after a prior irritant or *Candida* diaper dermatitis (see Chapter 16).⁵ Pustular psoriasis, either in a diffuse distribution or limited to

BOX 18.1 ERYTHRODERMAS: RED, SCALY BABY – DIFFERENTIAL DIAGNOSIS**INFLAMMATORY DISEASES**

- Atopic dermatitis
- Seborrheic dermatitis
- Psoriasis
- Acute generalized exanthematous dermatosis (AGEP)
- Pityriasis rubra pilaris
- Drug exanthem
- Boric acid poisoning
- Diffuse mastocytosis

INFECTIOUS DISEASES

- Staphylococcal scalded skin syndrome
- *Candida*/other fungal infections
- Herpes simplex virus
- Syphilis

GENODERMATOSES

- Netherton syndrome
- Autosomal recessive congenital ichthyosis (ARCI)
- Epidermolytic ichthyosis
- Sjögren–Larsson syndrome
- Chondrodysplasia punctata
- Ectodermal dysplasia

METABOLIC DISEASES

- Cobalamin deficiency
- Maple syrup urine disease
- Carbamoyl phosphate synthetase deficiency
- Argininosuccinic aciduria
- Methylmalonic aciduria
- Propionic acidemia
- Cystic fibrosis
- Essential fatty acid deficiency
- Holocarboxylase synthetase deficiency
- Biotinidase deficiency

IMMUNOLOGIC DISEASES

- Omenn syndrome
- DiGeorge anomaly
- Graft-versus-host disease
- Severe combined immunodeficiency
- Bruton hypogammaglobulinemia
- Common variable hypogammaglobulinemia
- Eosinophilic gastroenteritis



Figure 18.1 Seborrheic dermatitis: widespread erythema and scale.

the palms and soles, may be seen rarely. A positive family history for psoriasis is helpful. Some neonatal or infantile cases are HLA-B17 positive.⁶

Rarely, infantile psoriasis is generalized, a presentation that has been reported in young infants, and can even be present at birth. Erythroderma can evolve into and even alternate with pustulosis. Infantile generalized pustular psoriasis can be associated with lytic bone lesions,⁷ and be complicated by the acute respiratory distress syndrome (pulmonary capillary leak syndrome) that is also described in adults with acute generalized pustular psoriasis (B. Krafchik pers. comm.).⁸ Skin biopsy can be helpful in differentiating causes of neonatal erythroderma and in some cases, is diagnostic.⁴ Biopsy usually shows psoriasiform hyperplasia with elongated rete ridges and parakeratotic scale, often containing neutrophils. Occasionally, the diagnostic finding of a spongiform micropustule or microabscess in the upper epidermis is seen. Skin biopsies of erythrodermic psoriasis are often indistinguishable from those of any chronic dermatitis, lacking the classic features, and it may take several

biopsies and close observation over time to confirm the diagnosis.

Localized psoriasis may be treated with emollients and low-potency topical corticosteroids, but often clears only partially or recurs. Cases of infantile psoriasis may prove to be mild and occasionally even clear completely as the child gets older.⁹ The prognosis of generalized erythrodermic or pustular psoriasis in infancy is more guarded, and treatment usually requires systemic retinoid therapy, as well as supportive care.¹⁰

PITYRIASIS RUBRA PILARIS

Diffuse scale and erythema with palmoplantar keratoderma can suggest pityriasis rubra pilaris (PRP). Juvenile cases and even erythrodermic newborn presentations have been described.¹¹ Systemic therapy has been successful when indicated clinically.¹²

DRUG EXANTHEM

Erythroderma due to medications is fortunately rare, though cases in pediatric patients, including infants and neonates have been described.¹³ Severe reactions such as Stevens–Johnson syndrome or the drug reaction with eosinophilia and systemic symptoms (DRESS) represent particular challenges for clinicians.⁶ The approach to patients, regardless of age, requires a high index of suspicion and a broad understanding of other causes of erythroderma.¹⁴

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis (AGEP) presents acutely with pustules overlying diffuse erythema after exposure to an offending medication, mercury exposure or viral illness. Antibiotics reported to cause AGEP in infants include

amoxicillin and amoxicillin-clavulanic acid. AGEP has also been reported in infants with no antibiotic exposure, suggesting an infectious trigger in these cases.¹⁵ Subcorneal pustules are seen by skin biopsy (see [Chapter 20](#)).¹⁶

BORIC ACID POISONING

Boric acid poisoning is now very rare, but was seen in the past as a result of the frequent use of boric acid-containing powders and lotions for the treatment of diaper dermatitis. It presents with a maculopapular eruption that can evolve into a generalized erythroderma, the appearance of which has been likened to a boiled lobster. A report of this in an adult after ingestion of a boric acid-containing pesticide, has been published.¹⁷ A positive Nikolsky sign and desquamation are additional features. Like staphylococcal scalded skin syndrome, the condition may be accentuated in periorificial and intertriginous areas. Alopecia may also develop. Affected infants are usually ill, with fever, irritability, vomiting, and diarrhea, which can progress to shock and even death.

DIFFUSE CUTANEOUS MASTOCYTOSIS

The various forms of cutaneous mastocytosis are discussed fully in [Chapter 28](#). Only the rare diffuse cutaneous form of the disease is associated with neonatal erythroderma.¹⁸ The affected infant usually has generalized thickening of the skin, which can be subtle. The thickening is due to infiltration of the dermis by mast cells. Because these mast cells release histamine and other vasoactive substances, they cause the skin to be very reactive, with a tendency to develop erythema, flushing, and wheals. Urtication with minor trauma (Darier's sign), and blisters, which develop either spontaneously or superimposed upon wheals, may be seen. The absence of scale and the presence of the above findings differentiate mastocytosis from other causes of erythroderma. *C-kit* mutations are seen in most patients with systemic mast cell disease.¹⁸

Skin biopsy is diagnostic revealing a dense, band-like infiltrate of mast cells in the upper dermis, which can be confirmed with Giemsa stain.

Infectious diseases

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Staphylococcal scalded skin syndrome (SSSS) is an uncommon cause of neonatal erythroderma (see [Chapter 12](#)). It is characterized by the abrupt onset of diffuse erythema, which rapidly evolves to erosive desquamation involving most skin surfaces. Although there is often periorificial accentuation, giving a dry, chapped appearance, the staphylococcal toxin requires keratinizing epithelium and therefore spares mucous membrane surfaces. The toxins act at a subcorneal location due to effects on desmoglein 1.^{6,13} Epidermal sloughing, occurring with minor trauma, helps distinguish SSSS from the other causes of infantile erythroderma, with the exception of toxic epidermal necrolysis (TEN)¹⁹ (see [Chapter 12](#)) and boric acid poisoning (see above). Rarely, a widespread form of staphylococcal pustulosis has been observed acutely in otherwise healthy infants. The pustules develop on an erythematous macular base and are small and superficial. They subsequently desquamate, thereby mimicking a true erythroderma.

CANDIDIASIS

Candidal infection can cause neonatal erythroderma in two clinical settings: intrauterine acquisition with the development of congenital candidiasis, and postnatal onset in very premature infants. Congenital candidiasis typically presents either at birth or within the first few days of life with generalized erythema, vesicles, pustules, papules, and scaling. The pustules can be subtle at first, with erythroderma predominating. The palms and soles are often involved, which may be a helpful clue to diagnosis. The condition can occur in either term or preterm infants. *Candida albicans* can also cause a diffuse burn-like erythema within the first 2 weeks of life in premature infants (see [Fig. 14.5A](#));²⁰ Also diffuse scaling and erythema, most pronounced over the back may be seen.²¹ The diagnosis is made by examination of skin scrapings (KOH preparation) and/or surface culture for *Candida*, or by skin biopsy. The latter will show fungal elements within the epidermis and/or dermis, mixed inflammatory infiltrates, and occasional areas of necrosis and hemorrhage.

The risk of extracutaneous disease and the prognosis depend on the gestational age of the infant. In term infants, the prognosis is excellent, and topical anti-yeast therapies are usually curative. In infants weighing less than 1500 g with either congenital or acquired generalized cutaneous candidiasis, there is a significant risk of disseminated disease, and parenteral antifungal agents are recommended. Skin biopsies of affected areas in such infants may be used to predict the ultimate dissemination of disease. In one series, the finding of subcorneal invasion of *Candida* on skin biopsy was associated with a 69% risk for disseminated disease.²¹ Both conditions are discussed in more detail in [Chapter 14](#).

HERPES SIMPLEX

Although most cases of herpes simplex (HSV) infection have characteristic vesicular lesions localized on the presenting part, the so-called intrauterine variant of HSV can present at birth with either isolated or diffuse erythema, and scaling or crusted erosions on an erythematous base (see [Chapter 13](#)). It may be difficult to recognize clinically because vesicles may not be present.²² In fact, 44% of neonates with cutaneous disease do not have vesicles or bullae.²² This type of widespread involvement is generally associated with very severe neurologic disease. Multinucleated giant cells should be demonstrable on Tzanck smears of vesicular lesions. A skin biopsy, scrapings for direct fluorescent antibody staining, and viral cultures will help confirm the diagnosis.

SYPHILIS

Congenital syphilis may cause diffuse erythema and scaling (see [Chapter 12](#)). This presentation is most typically seen in infants 6–8 weeks of age, in whom exposure to syphilis occurred either very late in pregnancy or at the time of delivery.²³ Superficial erosions or bullae over the hands or feet of a newborn, together with a diffuse scaling dermatitis ([Fig. 18.2](#)), should alert the practitioner to the possibility of syphilis. Infiltrated mucosal papules and plaques (condyloma lata) may be seen in a perianal location and are similar to the mucous patches seen on other mucous membrane sites in older patients with secondary syphilis. Periosteal changes of long bones, such as the clavicles, as well



Figure 18.2 Diffuse superficial scaling and mild erythema involving the skin of an infant with congenital syphilis.



Figure 18.3 Diffuse erythema with fine scale in an infant with nonbulbous congenital ichthyosiform erythroderma.

as hepatosplenomegaly, are additional features. Appropriate serologies are generally diagnostic, and darkfield examination of mucous membrane lesions should reveal spirochetes.

Genodermatoses

ICHTHYOSIS

The ichthyoses are a group of genetic disorders characterized by generalized skin scaling; generalized erythroderma is a common presentation for some types of ichthyosis (see [Chapter 19](#)). Many infants with this presentation have the autosomal recessive congenital ichthyosis (ARCI) phenotype,²⁴ which is notable for either diffuse erythematous appearance of the skin and overlying fine white scale or thicker plate-like scale ([Fig. 18.3](#)). Ectropion can occur. Testing for *TGM1*, *ALOXE3*, *ALOX12B*, or *ICHTHYIN* genes can be done for individual cases (see [Chapter 19](#)). Infants with autosomal dominant bullous ichthyosis, epidermolytic ichthyosis (EI), typically present with diffusely erythematous skin and mild hyperkeratosis, often in association with areas of denuded skin. The lack of mucous membrane involvement in EI helps distinguish it from epidermolysis bullosa. Over subsequent weeks and months, the blistering subsides and is replaced by varying

degrees of an ichthyosiform erythroderma. Ultimately, marked hyperkeratosis is evident diffusely, with accentuation on flexural surfaces. The characteristic histopathologic findings of epidermal cytolysis of the upper spinous and granular layers help confirm the diagnosis of EI. Consideration of screening for mutations of keratins 1 and/or 10 is needed for confirmation.

The ichthyosis most likely to be confused with other causes of erythroderma is Netherton syndrome, a rare disorder caused by mutations in *SPINK5*, which encodes a serine protease inhibitor, LEKTI.²⁵ A publication has outlined specific mutations in *SPINK5* and the use of such data for prenatal diagnosis.²⁶ Some laboratories are able to stain tissue specimens for this protein.⁴ Netherton syndrome is marked by severe diffuse erythroderma, scaling, and varying degrees of alopecia, including sparse eyebrows ([Fig. 18.4](#)).^{27,28} Affected infants often fail to thrive as a result of the extreme metabolic demands presented by their skin disease, and they can also develop hypernatremic dehydration. Most have a markedly elevated IgE level. The diagnosis of Netherton syndrome is often delayed because of the late presentation of the diagnostic hair shaft abnormality, trichorrhexis invaginata (bamboo hair). Such hairs, when examined by routine light microscopy, will appear to have telescoped into themselves along the length of the shaft ([Fig. 18.5](#)). Small bulbous areas of thickening at the site of the telescoping correspond to the areas of increased fragility and ultimate breakage of affected hairs. Plucking of eyebrow hairs and evaluation of multiple areas of the scalp over time may be required to visualize the characteristic hair changes. Later in the course, patients may continue with generalized, scaling erythroderma or show a distinctive skin finding, ichthyosis linearis circumflexa. This is an erythematous scaling eruption with polycyclic and/or serpiginous morphology and elevated borders.

Sjögren–Larsson syndrome is due to a deficiency of fatty aldehyde dehydrogenase (FALDH) and can present with varying degrees of erythroderma.^{29,30} Most cases are due to mutations in the *ALDH3A2* gene, which codes for FALDH, though other factors play a role in some cases.³¹ A collodion membrane at birth is unusual. Affected infants may have a phenotype consistent with ARCI. Nonprogressive spasticity and mental retardation become apparent during the early years of life. After the first year, many affected patients have distinctive glistening dots seen on careful retinal examination.

Chondrodysplasia punctata (Conradi–Hünemann syndrome) presents with either diffuse erythroderma or bands of erythema, and a patterned ichthyosis occurring along Blaschko's lines ([Fig. 18.6](#)).^{32–34} Alopecia may be seen. These areas of ichthyosis typically resolve and may be replaced by a follicular atrophoderma. This X-linked dominant syndrome is also marked by skeletal defects (dwarfism), cataracts, and other features. Plain radiographs at the time of birth may show stippling of the epiphyseal areas of bones. It is due to a defect in emopamil binding protein (3 β -hydroxysteroid- Δ 8, Δ 7-isomerase).

Infantile erythroderma can also be seen in keratosis–ichthyosis–deafness (KID) syndrome,^{35,36} and neutral lipid storage disease with ichthyosis (Chanarin–Dorfman syndrome).^{37,38} A report of erythroderma as a presenting sign of Menkes disease has been published.³⁹

Occasionally, males affected with X-linked hypohidrotic ectodermal dysplasia may present at birth with a mild diffuse erythroderma and fine superficial scaling ([Fig. 18.7](#)).⁴⁰ Such infants have the typical facial features of ED and sparse hair, lashes, and eyebrows. Periorbital hyperpigmentation and fine



Figure 18.4 Netherton syndrome: diffuse erythema, scale, and alopecia.



Figure 18.5 Hair from patient with Netherton syndrome illustrating trichorrhexis invaginata.

wrinkling can be seen at birth, and lateral plain films of the skull will demonstrate no or few tooth buds (Fig. 18.8). Some of these patients have been reported to have primary immunodeficiency as well.^{41,42}

Immunologic diseases

Several immunologic diseases marked by immunodeficiency may produce similar initial clinical signs, with an eczematous dermatitis, diarrhea and failure to thrive. Children with a persistent eczematous eruption accompanied by failure to thrive may warrant an immunologic evaluation. The following discussion encompasses immunodeficiency syndromes with either erythroderma or other cutaneous manifestations in the neonatal period. These are outlined in Table 18.1.

ERYTHRODERMA AND FAILURE TO THRIVE

In 1988, Glover and colleagues⁴³ reported a group of five infants with erythroderma, diarrhea, and failure to thrive. None had a yeast opsonization defect (as described in so-called 'Leiner disease'), however, a variety of other immunologic abnormalities, including elevated IgE levels and hypogammaglobulinemia, were found. Some patients were subsequently diagnosed as having Netherton or Omenn syndromes. This paper established the need to consider the diagnosis of immunodeficiency when evaluating erythrodermic infants, and established the multiple etiologies of what had formerly been called Leiner disease.

Infants in this category have a clinical phenotype of (1) noncongenital or acquired erythroderma (Fig. 18.9); (2) diarrhea; and (3) failure to thrive. Infants with these findings need thorough investigations searching for the underlying cause of their disorder. Most of the diseases listed in Box 18.1 need to be considered, especially immunodeficiencies, Netherton syndrome, Omenn syndrome, and eosinophilic gastroenteritis (see below). Baseline immune studies of such infants should include chest radiograph, full blood count, quantitative immunoglobulins, and specific measures of T-cell function. More detailed testing should be pursued as indicated.

The prognosis and treatment of this condition are entirely dependent on the specific diagnosis. The associated diarrhea and failure to thrive must be treated aggressively with adequate nutritional support up to and including parenteral hyperalimentation, as indicated.

SEVERE COMBINED IMMUNODEFICIENCY

Severe combined immunodeficiency (SCID) is a heterogeneous group of inherited disorders with similar clinical manifestations and immunologic deficiencies, with a profound deficiency of T lymphocytes and defects in both cellular and humoral immunity. Subtypes are classified by the abnormal development of other lymphocyte lineages, predominantly B lymphocytes and



Figure 18.6 (A) Diffuse cutaneous erythema with patterned hyperkeratosis over the back of a female with Conradi-Hünermann syndrome. (B) The same infant showing more pronounced hyperkeratosis over the right lower extremity.



Figure 18.7 Mild diffuse cutaneous erythema and very superficial scaling on a child with X-linked hypohidrotic ectodermal dysplasia. These findings were present at birth.



Figure 18.8 A lateral skull film from the same male neonate in Figure 18.7, showing the absence of tooth buds.

natural killer (NK) cells. Most cases are inherited in an autosomal recessive manner, although approximately 40% are X-linked recessive. About 20% of SCID cases are caused by adenosine deaminase (ADA) deficiency.⁴⁴ Several other genetic defects account for the balance of causes of SCID.⁴⁵

The immunologic deficiency results in an increased susceptibility to bacterial, viral, fungal and protozoan infections. Recurrent infections, diarrhea, and failure to thrive are evident by 3–6 months of age.⁴⁶ Among the most common mucocutaneous infections are those due to *Candida albicans*, *Staphylococcus aureus*, and *Streptococcus pyogenes*. In addition to infectious cutaneous manifestations, all reported forms of SCID can present with a diffuse skin involvement, either erythroderma (Fig. 18.10), morbilliform, or seborrheic dermatitis-like eruptions. Patients with SCID may develop graft-versus-host disease from nonirradiated blood products or engraftment of maternal lymphocytes (Fig. 18.11). Cutaneous manifestations vary from a morbilliform rash or exfoliative dermatitis in acute GVHD, to a lichenoid or sclerodermoid rash in chronic GVHD. Early extracutaneous infections may also include viral-induced

chronic diarrhea, otitis media, and pneumonia due to bacteria, viruses or *Pseudomonas carinii*.

The prognosis of SCID is poor and, without intervention, most patients die from overwhelming infection by 1 year of age. The importance of early diagnosis cannot be overemphasized. Some states screen newborns for SCID on a routine basis.^{45,47} Screening for T-cell receptor excision circles (TRECs) has been useful as a screen for SCID when neonates are found to have unusually low lymphocyte counts. TRECs are biomarkers for new and naive T cells.⁴⁵ Follow-up testing for more specific genetic causes of SCID can be done based upon this test which can be done by routine newborn blood screening.⁴⁸ Management includes protective isolation and vigorous treatment of infections. All blood products should be irradiated to prevent GVHD. Hematopoietic stem cell transplantation is the

TABLE
18.1

Immunodeficiency syndromes with cutaneous manifestations in the neonatal period

Immunodeficiency	Cause/gene	Infectious organisms	Cutaneous findings	Associated findings
Severe combined immunodeficiency (SCID)	<i>IL2RG</i> , <i>ADA</i> , <i>IL7R</i> , <i>JAK3</i> , <i>RAG</i>	Bacterial (<i>S. aureus</i> , <i>Strep. pyogenes</i>) Viral Fungal (<i>C. albicans</i>) Protozoan Same as SCID	Erythroderma Morbilloform Seborrheic dermatitis-like GVHD Erythroderma Alopecia	Diarrhea Failure to thrive Pneumonia
Omenn syndrome	<i>RAG</i> gene mutation			Lymphadenopathy Hepatosplenomegaly Failure to thrive Elevated IgE, eosinophilia Thymic aplasia/hypoplasia Cardiac anomalies Hypoparathyroidism Cleft palate
DiGeorge anomaly	Microdeletion 22q11 <i>JBX1</i> gene Deletion 10p14	Fungal Viral <i>Pneumocystis carinii</i>	Ecematous dermatitis Erythroderma GVHD	Thrombocytopenia Autoimmune disease Lymphoreticular malignancy Sinopulmonary infections Elevated IgE Bone fractures Long-term risk of malignancy
Wiskott–Aldrich syndrome	<i>WAS</i> gene	Bacterial Viral <i>Pneumocystis carinii</i> <i>S. aureus</i> <i>Candida</i>	Ecematous dermatitis Petechiae, purpura Severe dermatitis Abscesses	Pulmonary infections Hepatic abscesses Hepatosplenomegaly
Hyperimmunoglobulin E syndrome (HIES) (AD HIES)	<i>STAT3</i> mutations			
<i>DOCK8</i> deficiency (AR HIES)	<i>DOCK8</i> mutation	HSV, molluscum, fungal	Severe dermatitis, vesicles, papules	
Chronic granulomatous disease	Impaired phagocyte killing NADPH oxidase genes (<i>CYBB</i> , <i>CYBA</i> , <i>NCF1</i> , <i>NCF2</i> , <i>NCF4</i>)	Bacterial Fungal (<i>Aspergillus</i>)	Granulomas	



Figure 18.9 Diffuse erythroderma and scaling with failure to thrive in an infant with hypogammaglobulinemia.

treatment of choice. Enzyme replacement with ADA coupled to polyethylene glycol (PEG-ADA) has helped several infants with ADA deficiency, and ADA is a target for gene therapy protocols. However, enzyme replacement alone may not be sufficient.^{44,49}

OMENN SYNDROME

Omenn syndrome is a rare autosomal recessive form of SCID with reticuloendothelial cell proliferation caused by



Figure 18.10 Erythema and scaling is seen in the exfoliative phase of GVHD.

recombinase-activating gene (*RAG1* or *RAG2*) deficiency in most patients. This syndrome was originally described as familial reticuloendotheliosis with eosinophilia. This T-cell deficient state is marked by abnormal histiocytic cells and extreme elevations of eosinophils in affected tissues and in the peripheral blood. During early infancy these patients develop a generalized exfoliative erythroderma (Fig. 18.12), lymphadenopathy, hepatosplenomegaly, recurrent infections, and failure to thrive.⁵⁰ Diffuse alopecia may be seen as well. Although the condition is primarily one of T-cell dysregulation, both humoral and cellular immune defects are seen.⁵¹ Abnormal antibody production and elevated IgE levels occur. There is usually a marked leukocytosis with eosinophilia, anemia, hypogammaglobulinemia, and depressed T-cell mediated immunity. As noted above, *RAG1* or *RAG2* gene mutations are seen in most cases of Omenn syndrome. These result in faulty T- and B-cell development. Other gene mutations exist in this syndrome.⁵¹ The disorder is often difficult to distinguish from GVHD by skin biopsy.⁴ The only known effective treatment is bone marrow transplantation.



Figure 18.11 A male child diagnosed with SCID. He manifested a diffusely distributed blanching erythema. The skin eruption was caused by post bone-marrow transplant GVHD.

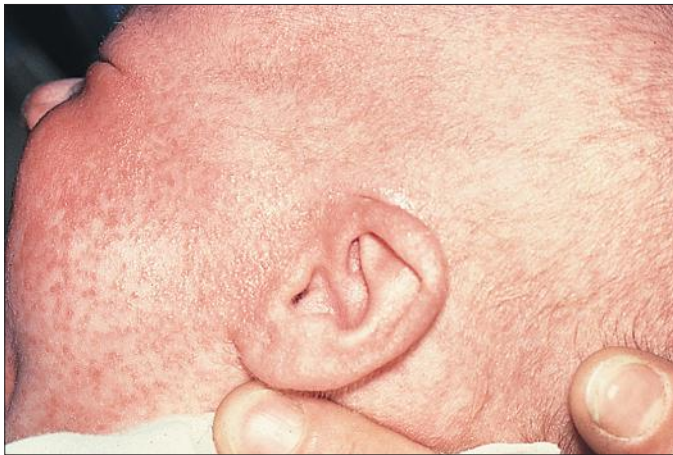


Figure 18.12 A child diagnosed with Omenn syndrome, illustrating diffusely distributed, scaling, erythematous papules. These findings were present over the entire skin surface.

DIGEORGE ANOMALY

The DiGeorge anomaly (DGA) is one of a group of disorders that have in common a chromosomal deletion resulting in monosomy 22q11, known as the DiGeorge syndrome chromosome region, or DGCR. A small fraction of patients with clinical features of DGA have deletions of chromosome 10p14.⁵² Autosomal dominant, autosomal recessive and X-linked inheritance have all been reported. All forms are associated with a T-cell defect and normal humoral immunity. The compromise in T-cell production is a result of thymic hypoplasia or aplasia, which is in turn part of a larger developmental anomaly of the third and fourth pharyngeal pouches. In addition to the thymus defect, conotruncal cardiac anomalies, hypoparathyroidism, dysmorphism, and cleft palate are prominent features.

Characteristic facial features include a short philtrum, low-set ears, and hypertelorism.⁵³ Neonatal tetany may occur with hypocalcemia due to aplastic parathyroid glands. Also mapping to 22q11 is the velocardiofacial syndrome which shares many of these features as well as mental disorders. Many such cases are due to mutations in the *TBX1* gene. These disorders are part of a spectrum.⁵⁴

Infants with DiGeorge syndrome can have a maculopapular or eczematous dermatitis that may become generalized.^{55,56} A group of patients with incomplete DiGeorge syndrome and diffuse eczematous dermatitis have been studied by histopathology. Findings included dyskeratosis of keratinocytes, satellite cell necrosis, and parakeratosis with neutrophils.⁵⁷ Many patients have recurrent mucocutaneous candidal infections as neonates, as well as increased susceptibility to viral, *Pneumocystis carinii* and fungal infections. GVHD may occur in patients who are given nonirradiated blood products. Noninfectious granulomas have also been described. Patients with DGA may have erythroderma, similar to that seen in Omenn syndrome, which occurs in association with a dramatic oligoclonal expansion of a few founding T-cells, often of an exclusively memory type.⁵⁸ No live vaccines should be given and blood products should be irradiated. Patients with dramatically low levels of T-cells should be considered for an HLA-identical bone marrow transplant or a thymus transplant.⁵⁸

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease (GVHD) is caused by the interaction between immunocompetent lymphoid cells and immunodeficient host cells.⁵⁹ Nearly all cases in neonates and young infants are caused by severe T-cell immunodeficiency states (such as severe combined immunodeficiency) with maternal engraftment either in utero or at the time of delivery.⁶⁰ Clinically, affected infants typically present with scaling and erythema that often begin on the scalp and face and moves downward. Fine erythematous papules may also occur. The findings may be patchy or diffuse, in some cases progressing to frank erythroderma (Fig. 18.10).⁶⁰ The most extreme cutaneous manifestation of GVHD is severe, generalized desquamation, a finding that may rarely be evident at the time of delivery. Diffuse alopecia is a common finding and often involves the eyebrows as well as scalp hair. Although milder forms of GVHD sometimes respond (at least partially) to emollients or topical corticosteroids, recurrences are the rule. If unrecognized and untreated, GVHD progresses and may affect a variety of organ systems.

The diagnosis should be suspected in any young infant with erythroderma and frequent infections, chronic diarrhea, and/or failure to thrive. If present, a family history of prior early infant deaths is helpful because many forms of immunodeficiency are familial. Skin biopsy can be very useful in confirming the diagnosis. The histopathologic changes of GVHD are usually graded by severity (from I to IV).⁶¹ Most authors agree that minimum criteria for the histopathologic diagnosis of GVHD include the presence of epidermal lymphocytes, dyskeratosis, and satellite cell necrosis. The latter refers to the finding of a lymphocyte apposed to an eosinophilic keratinocyte (dyskeratotic epidermal cell) within the epidermis. Similar changes may also result from the conditioning therapy utilized for some patients before bone marrow transplantation, as well as from the effect of certain viruses.⁶² In some cases of GVHD caused by maternal

engraftment, a spongiotic dermatitis may predominate.^{60,63} Multiple skin biopsies obtained over days or weeks may be necessary if the diagnosis is strongly suspected, but without confirmatory histopathology.⁴ Immunophenotyping of skin biopsies has been used to complement the characteristic findings on routine histopathology described previously.⁶⁴ It should be emphasized, however, that immunophenotyping alone should not be considered diagnostic of GVHD, and that the lack of such features should not discount the presence of compatible clinical and histopathologic findings of this condition.

Because the diagnosis of GVHD in the absence of a known organ or bone marrow transplant implies a severe immunodeficiency, a complete evaluation of the immune system should be undertaken. Although lymphopenia is characteristic of severe T-cell or severe combined immunodeficiency, the lymphocyte count in the blood may be normal or even elevated because of the presence of circulating maternal lymphocytes. Eosinophilia is often present. Although small numbers of circulating maternal cells are considered a normal finding in the first few weeks of life, the presence of large numbers of maternal lymphocytes is highly suggestive of an underlying immunodeficiency, and in the setting of erythroderma, strongly suggests the diagnosis of GVHD. Maternal engraftment can be documented by performing analysis for chimerism to demonstrate maternal T lymphocytes.⁶

The differential diagnosis is generally confined to other more common conditions, such as seborrheic dermatitis, infantile atopic dermatitis, or the unusual viral or drug eruptions.

The course of this condition can be variable and depends on the degree of organ involvement, as well as the severity of the immunodeficiency. In most instances, the skin can be treated with bland emollients, as well as low- or mid-potency topical corticosteroid preparations. More severe reactions, particularly those with systemic manifestations, may require systemic corticosteroid therapy, cytotoxic drugs, or monoclonal antibodies.⁵⁹ For subacute or chronic skin disease, in the absence of systemic involvement, phototherapy, either PUVA or narrow-band UVB, has proven useful both as a primary therapy and as a means to decrease or discontinue altogether the use of systemic therapies.^{65,66} Such therapy is usually reserved for older patients.

The skin manifestations of GVHD occurring after transplantation, or rarely resulting from transfusions, have been well-characterized and are varied. They include an acute phase with morbilliform erythema, papular dermatitis, diffuse erythroderma, or in severe cases, diffuse bullae or frank necrosis, such as are seen in toxic epidermal necrolysis. Often, such skin changes begin on the head and neck and extend in a caudal fashion. The palms and soles are predominantly involved. Chronic changes (more than 100 days post-transplantation) may include oral mucous membrane changes, nail dystrophy, and localized or diffuse lichenoid (flat-topped) papules. Extracutaneous features of the disease are primarily gastrointestinal. Hepatitis may be found, as well as varying degrees of diarrhea. Skin biopsies of representative lesions will generally reveal features of GVHD, as described above.

WISKOTT-ALDRICH SYNDROME

Wiskott-Aldrich syndrome (WAS) is a rare X-linked recessive disorder characterized by recurrent pyogenic infections,

bleeding due to thrombocytopenia, and recalcitrant eczematous dermatitis. The gene for WAS has been mapped to chromosome Xp11²⁸ and encodes for WAS protein (WASP), a cytoplasmic protein constitutively expressed in all hematopoietic stem cell-derived lineages.⁶⁷

The most consistent finding in WAS is thrombocytopenia with small platelets. Because it is present from birth, initial presenting signs in the majority of patients are related complications such as petechiae, purpura, epistaxis, gastrointestinal bleeding, or intracranial hemorrhage.⁶⁸ Recurrent bacterial infections begin in infancy and include otitis media, pneumonia, infectious diarrhea, sinusitis, meningitis, and septicemia. There is also increased susceptibility to viruses and *Pneumocystis carinii*. There is also an increased risk of autoimmune disease and malignancy, mainly lymphoreticular malignancies.⁵² Laboratory examination may also reveal characteristic elevated IgA and IgE and decreased IgM.⁶⁷

Dermatitis usually develops during the first few months of life and meets the criteria for atopic dermatitis (see Fig. 15.16). The face, scalp, and flexural areas are usually the most severely involved, although involvement can be widespread. Of patients with WAS, 80–100% will have eczematous skin disease, which can be widespread and difficult to control.⁶⁹ Excoriated areas often have associated petechiae or purpura, and secondary bacterial infection of eczematous lesions is common, as are eczema herpeticum and molluscum.⁵² Other infections of the skin may be present independently, and may include impetigo, cellulitis, and abscesses.

Treatment is largely symptomatic and includes antibiotics and intravenous immunoglobulin in selected cases. Splenectomy may be used to treat thrombocytopenia, although there is an increased risk of post-splenectomy sepsis. Platelet transfusion is reserved for cases of life-threatening hemorrhage.⁵² Blood products should be irradiated. At present, bone marrow transplant or cord blood stem cell transplant is the only curative therapy for WAS.⁶⁸

HYPERIMMUNOGLOBULIN E SYNDROME

Hyperimmunoglobulin E (hyper-IgE) syndrome (HIES), formerly also known as Job syndrome, consists of a severe dermatitis with recurrent abscess formation and recurrent sinopulmonary infections associated with markedly elevated serum IgE levels.⁷⁰ Inheritance follows an autosomal dominant pattern with variable penetrance. *STAT3* mutations are the cause of the majority of autosomal dominant HIES.³

The severe dermatitis may be present from birth or early childhood, and as in atopic dermatitis, the rash is typically pruritic and often lichenified, although its distribution may be atypical for true atopic dermatitis (see Fig. 15.17). A distinct papulopustular eruption of the face and scalp has been reported in the first year of life (see Fig. 10.28).⁷¹ A history of allergic diseases, absence of bone or joint abnormalities, or deep-seated abscesses suggests atopic dermatitis rather than HIES.⁷²

Cutaneous infections are frequent and start in infancy. They may take the form of crusted plaques, pustules, furuncles, cellulitis, lymphangitis, or abscesses. The abscesses may be erythematous and tender, or may be fluctuant masses which are neither hot nor tender and are not associated with systemic symptoms ('cold abscesses'). They are filled with pus that grows *Staphylococcus aureus* on culture. This diagnosis should be

considered in children with recurrent abscesses complicating chronic eczema. Skin biopsy reveals an eosinophilic infiltrate similar to that seen in eosinophilic pustular folliculitis. Infection with nonbacterial pathogens may also occur, especially *Candida* infections of the mouth, nails, and skin.⁷³

In addition to skin infections, sinopulmonary and bone infections are common. *S. aureus* is also the most common organism for these infections. Skeletal abnormalities, including hyperextensible joints, are seen in hyper-IgE syndrome.⁷³ Coarse facial features manifested by a prominent forehead and a broad nasal bridge are typically not seen at birth but appear later in childhood. Patients with viral infections such as warts, molluscum, or severe/recurrent HSV with atopic dermatitis should be considered for *DOCK8* deficiency. Such patients also have an increased risk for malignancies such as squamous cell carcinoma and lymphoma.^{2,3}

The management of hyper-IgE syndrome includes prophylactic antibiotics to prevent *S. aureus* infections. The eczematous dermatitis may require treatment with topical corticosteroids to reduce inflammation and antihistamines to control pruritus. Incision and drainage may be required for abscesses.⁷⁴

CHRONIC GRANULOMATOUS DISEASE

Chronic granulomatous disease (CGD) represents a group of genetic disorders in which impaired intracellular microbial killing by phagocytes leads to recurrent bacterial and fungal infections and granuloma formation. Defects in the nicotinamide dinucleotide phosphate (NADPH) oxidase complex result in failure to generate superoxide radicals during the respiratory burst, leading to an inability of phagocytic lymphocytes to kill intracellular bacteria and fungi, especially *Aspergillus* spp. CGD can be caused by mutations in any of the five structural genes of NADPH oxidase. The most common type is X-linked recessive, and the remainder are autosomal recessive.⁷⁵ Of genetic mutations, 70% are of the *CYBB* gene resulting in the X-linked form of CGD.⁷⁶

The earliest lesions are usually staphylococcal infections of the skin around the nose and mouth, which may be present at birth. Skin abscesses, usually caused by *S. aureus*, occur in 42% of patients. Purulent inflammatory reactions may occur at sites of minor cutaneous trauma or sites of regional lymph node drainage with suppurative lymphadenitis. There are also reports of cutaneous granulomas containing the typical pigmented macrophages also seen in visceral granulomas.⁷⁷

The extracutaneous organs most frequently involved are the lymph nodes, lungs, and liver. Bronchopneumonia is the most prevalent infection, with abscess formation and empyema as frequent complications. These patients have hepatosplenomegaly, and granulomas of the liver and spleen are common. Hepatic abscesses are usually caused by *S. aureus* and may require surgical drainage.

In the past, the screening test for CGD is the nitroblue tetrazolium (NBT) reduction assay. The dihydrorhodamine (DHR) test has become the more frequently used testing method. This measures NADPH oxidase activity by flow cytometry.⁷⁶ Management includes antibacterial and antifungal prophylaxis and treatment. Patients with all forms of CGD have shown clinical improvement after administration of subcutaneous recombinant IFN- γ .⁷⁸ Allogeneic hematopoietic stem cell transplantation is curative.

EOSINOPHILIC GASTROENTERITIS

Eosinophilic gastroenteritis was first reported by Waldman and colleagues^{79,80} who called the condition allergic gastroenteropathy. Cutaneous features included edema, particularly over the face, as well as generalized atopic dermatitis. The extracutaneous manifestations are striking and include growth retardation, extreme hypoalbuminemia, hypogammaglobulinemia, anemia, and eosinophilia, as well as mild gastrointestinal symptoms consisting of intermittent diarrhea or vomiting after the ingestion of certain foods, and excessive loss of protein into the gastrointestinal tract.⁸¹ Asthma and allergic rhinitis may also be present. Diagnosis is confirmed with intestinal biopsies, which reveal mucosal eosinophilia. The disease is now subclassified into protein-sensitive and idiopathic forms.⁸² The protein-sensitive form is more common, responds to dietary restriction of cow's milk or soy protein, and ultimately resolves with time. The idiopathic form requires steroid therapy to control symptoms. The dermatitis improves rapidly and dramatically with resolution of the other symptoms when the dermatitis is aggressively treated.

Metabolic disorders

Disorders of metabolism (Table 18.2) often present during the neonatal period and may exhibit skin manifestations. Rarely, metabolic diseases are associated with erythroderma, either shortly after birth, or later resulting from subsequent therapeutic dietary restrictions. Although cutaneous manifestations may be seen with such diseases, many metabolic disorders manifest with feeding or neurological abnormalities, or through biochemical abnormalities alone.^{83,84} Lysosomal

TABLE
18.2

Classification of inherited metabolic disorders

Organic acid disorders	Fatty acid disorders	Amino acid disorders	Others
BKT	MCAD	PKU	BIOT
GA 1	VLCAD	MSUD	GALT
HMG	LCHAD	HCY	CF
MCD	CUD	CIT	LSD
IVA		ASA	
MUT			
3MCC			
Cb1 A, B			
PROP			

BKT, b-ketothiolase deficiency; GA-1, glutaric acidemia, type 1; HMG, 3-OH 3-CH3 glutaric aciduria; MCD, multiple carboxylase deficiency; IVA, isovaleric acidemia; MUT, methylmalonic acidemia (mutase deficiency); 3MCC, 3-methylcrotonyl-CoA carboxylase deficiency; Cb1 A, B, methylmalonic acidemia (cobalamin 1 A, B); PROP, propionic acidemia; MCAD, medium-chain acyl-CoA dehydrogenase deficiency; VLCAD, very long-chain acyl-CoA dehydrogenase deficiency; LCHAD, long-chain L-3-OH acyl-CoA dehydrogenase deficiency; CUD, carnitine uptake defect; PKU, phenylketonuria; MSUD, maple syrup urine disease; HCY, homocystinuria; CIT, citrullinemia; ASA, argininosuccinic-CoA lyase deficiency (argininosuccinic aciduria); BIOT, biotinidase deficiency; GALT, classic galactosemia; CF, cystic fibrosis; LSD, lysosomal storage disease.

Modified from Seashore MR, Seashore CJ. Newborn screening and the pediatric practitioner. *Semin Perinatol* 2005; 29:182–8.

storage diseases may present with coarse facial features as well as organomegaly.

Many metabolic conditions have been well-described over the last several decades and are now associated with documented molecular bases. Due to the similarity of skin findings seen with this group of disorders, the term acrodermatitis dysmetabolica has been suggested.⁸⁵ This describes diffuse and/or periorificial scale and erythema.

Organic acid disorders

METHYLMALONIC ACIDEMIA

Methylmalonic acidemia (MMA) is an inborn error of metabolism inherited in an autosomal recessive manner.⁸⁶ It includes a group of diseases caused by a defect in the metabolism of branched-chain amino acids, which results in the accumulation of methylmalonic acid. Although some cases of methylmalonic acidemia, especially those caused by a cobalamin F and cobalamin C type of defect, have presented with a dermatitis similar to that seen in acrodermatitis enteropathica,⁸⁶ more commonly the dermatitis begins after the institution of dietary restrictions.⁸⁷ In either case, the appearance is similar and in a primarily periorificial location. There are erythema and ulceration in the corners of the mouth and genital areas. A more diffuse dermatitis resembling SSSS has also been described. Extracutaneous manifestations can include poor feeding, vomiting, hypotonia, and acidosis, often leading to coma and death.

Assays for serum amino acid and metabolic analysis of cultured skin fibroblasts from affected patients confirm the diagnosis. Urinary organic acids should also be examined for elevations of methylmalonate and homocystine. Enzyme analysis in white cells or fibroblasts or mutation analysis can be used for confirmation of this diagnosis.⁸⁸ Skin biopsy shows vacuolar dermatitis with dyskeratotic keratinocytes, mild psoriasiform changes, and epidermal pallor as seen in acrodermatitis enteropathica. There is a lymphocytic perivascular infiltrate within the dermis, as well as areas of orthokeratosis and parakeratosis, with spongiosis of the epidermis. The differential diagnosis of this disease includes other metabolic and nutritional deficiency states, such as acrodermatitis enteropathica, other aminoacidurias, and biotinidase deficiency. Management consists of dietary restrictions of branched-chain amino acids, specifically isoleucine and valine, and, in those cases marked by cobalamin deficiency, supplementation with cobalamin. The prognosis of MMA is guarded, with many patients remaining severely impaired neurologically in spite of aggressive dietary support.

Fatty acid disorders

ESSENTIAL FATTY ACID DEFICIENCY

Essential fatty acid (EFA) deficiency was seen more frequently before 1975, in patients on parenteral hyperalimentation, before the need for EFA supplementation was recognized. It is now an extremely unusual condition though reports continue to exist in this setting.⁸⁹ It presents with a diffuse fine desquamation and mild or even absent erythema. The condition sometimes occurs in patients with severe fat malabsorption and may be one of the causes of the dermatitis of cystic fibrosis.

Amino acid disorders

MAPLE SYRUP URINE DISEASE AND OTHER INBORN ERRORS OF METABOLISM

In maple syrup urine disease (MSUD),^{90–92} diffuse exfoliative erythroderma has been well described. MSUD is another inborn error of metabolism in which the metabolism of branched-chain amino acids is defective. There is an abnormality in the degradation of the branched-chain amino acids causing diagnostic elevations of isoleucine, leucine, and valine in the serum, as well as in urine and cultured tissue fibroblasts. Again, enzyme analysis of WBC or fibroblasts or mutation analysis will confirm this diagnosis.⁸⁸ An erythematous scaling eruption that becomes erosive begins in a primarily periorificial distribution within days after initiating dietary therapy. The eruption is similar to that seen in acrodermatitis enteropathica. It can generalize, however. Such infants may also present with poor feeding, vomiting, lethargy, and seizures. Death may occur if the disorder is not promptly recognized. The skin disease may be caused by low isoleucine levels due to the dietary restrictions required for the disease. A similar, albeit milder dermatitis has been induced in infants fed diets deficient in isoleucine,⁹³ and similar eruptions have also been noted in citrullinemia,⁹⁴ carbamoyl phosphate synthetase deficiency, and argininosuccinic aciduria.⁹⁵ The cause of the dermatitis in each of these cases is also presumed to be caused by an abnormality of branched-chain amino acids, such as isoleucine. Histopathology of skin biopsies may show a very superficial perivascular lymphohistiocytic infiltrate with erosion of the outer epidermis, again as may be seen in skin biopsies from patients with other inborn errors of metabolism. The differential diagnosis includes other organic acidemias in which periorificial dermatitis may occur after initiation of dietary therapy, such as propionic acidemia and methylmalonic acidemia (Fig. 18.13). Treatment requires diligent attention to dietary restrictions. The diet must be liberalized so that sufficient branched-chain amino acids are delivered to raise plasma concentrations above the subnormal range.



Figure 18.13 An infant with tyrosinemia and zinc deficiency presents with perineal scaly plaques similar to the eruption seen in acrodermatitis enteropathica.

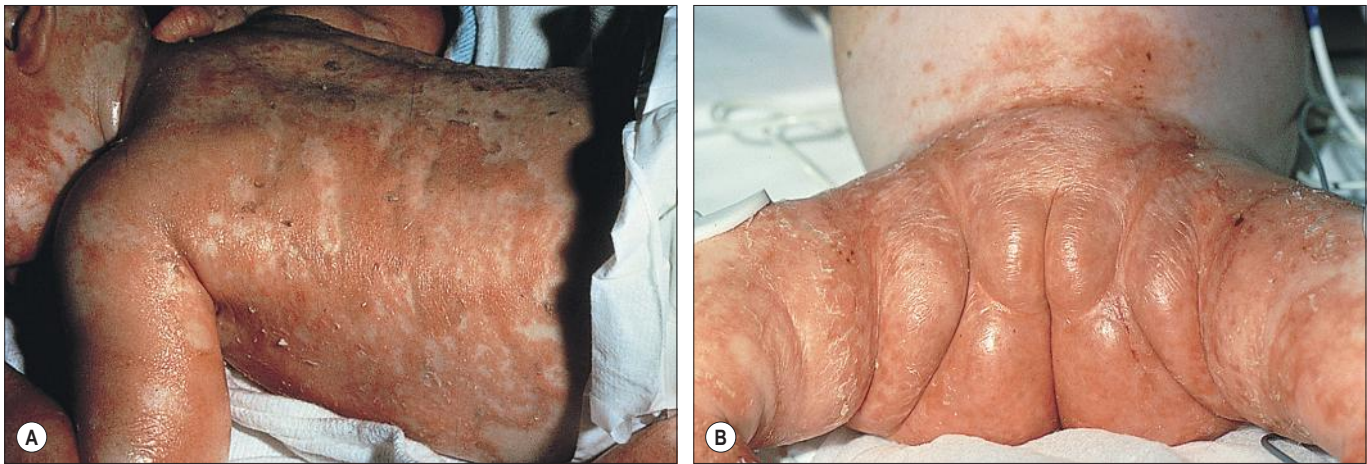


Figure 18.14 (A) Diffuse erythroderma and scaling on an infant later diagnosed with cystic fibrosis. (B) A different infant with periorificial erythema and scale. This child was also later diagnosed with cystic fibrosis.

CYSTIC FIBROSIS

Infants with cystic fibrosis (CF) can develop widespread, scaly erythematous lesions as a manifestation of global malnutrition during the first 3 or 4 months of life, and these are occasionally the initial presentation of CF.^{96–99} The dermatitis is variable. A diffuse erythematous papular dermatitis, diffuse desquamating erythema, a distinctly periorificial erythema and scaling or, commonly, a generalized desquamative erythroderma may be seen (Fig. 18.14). The dermatitis does not respond completely to treatment with topical corticosteroids or antifungals. In contrast to infants affected with classic acrodermatitis enteropathica, infants with cystic fibrosis typically lack paronychia involvement. Affected infants often have depressions of zinc levels, increased liver transaminases, and normal or slightly depressed levels of alkaline phosphatase. The dermatitis of CF occasionally clears with zinc therapy, but does so more reliably with appropriate enzyme replacement and nutritional supplements. The etiology of the dermatitis is likely multifactorial with data suggesting zinc, essential fatty acid, and protein deficiencies.⁹⁹

Testing for metabolic diseases

With the abundance of diagnostic testing for metabolic diseases, many are now currently included in mandated state newborn screening programs. Newborn screening began with testing for phenylketonuria (PKU) in 1940 and – in addition to hypothyroidism – might include only galactosemia routinely. Testing availability varies by locality. The Secretary of the US Department of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children has suggested a uniform screening panel of 31 core disorders.¹⁰⁰ The importance of such screening is intervention at a time in advance of the often devastating consequences of these disorders. Many of these disorders will present during the first week of life with metabolic acidosis and/or hyperammonemia, as well as altered neurologic status or emesis. Such findings are nonspecific and may be initially diagnosed as sepsis. Severe mental status alteration, however, should be a clue to a primary metabolic disease. Extreme elevations in the anion gap will suggest organic acidemias, such as propionic acidemia, methylmalonic acidemia, isovaleric acidemia, or multiple carboxylase deficiency. Elevations in serum ammonia levels may be a sign of the

organic acid disorders, as well as urea cycle abnormalities, mitochondrial diseases, or disorders of fatty acid β -oxidation. Table 18.3 lists diseases to be considered when a clinical or laboratory finding is present, along with suggested testing.

Many of these disorders now have well-described molecular diagnoses. Most are inherited in either autosomal recessive or X-linked recessive fashion. Basic screening tests include plasma amino acid levels and urine organic acids. Screening for acylcarnitine levels can provide clues to both organic acidurias and fatty acid oxidation disorders, such as medium-chain acyl-CoA dehydrogenase deficiency (MCAD). Serum amino acid studies will diagnose disorders such as maple syrup urine disease and homocystinuria. More specific testing is required for disorders such as biotinidase deficiency, galactosemia, cystic fibrosis, peroxisomal, or lysosomal storage diseases. As noted above, specific enzyme analysis and confirmatory testing is available for most biochemical defects.⁸⁸ Clinicians caring for infants should be aware of the often broad and nonspecific presentation of metabolic disorders and work closely with genetic/metabolic consultants. The goal of prompt diagnosis and treatment is to attempt to avoid the severe long-term sequelae of neurologic deficits or death.

Evaluation and management of the red scaly baby

The history and physical examination may provide important diagnostic clues to the etiology of erythroderma. Specific parameters that may be of value in determining an underlying cause include: congenital onset, skin induration, and the presence of large scaling plaques, alopecia with or without hair dysplasia, evolution, response to corticosteroid therapy, presence of infections, and failure to thrive.^{6,13,101} If the infant appears to have atopic or seborrheic dermatitis, then appropriate therapy can be instituted. If there is no response to therapy, or if the infant appears to be systemically ill, fails to thrive, or shows other evidence of a more generalized disease, a more comprehensive evaluation should be undertaken (Boxes 18.1, 18.2 and Fig. 18.15). Laboratory tests useful in evaluating erythroderma in neonates and infants are outlined in Box 18.2. The selection of which tests to perform depends on which disease(s) are most suspected. Appropriate smears and cultures for fungal, bacterial, or viral disease

TABLE 18.3**Clinical clues to metabolic disorders**

Clinical sign/Lab finding	Differential diagnosis	Suggested testing
Metabolic acidosis without lactic acidosis or ketonuria	Pyroglutamic aciduria	Urine organic acids Molecular testing
Metabolic acidosis without lactic acidosis, with ketonuria	Organic acidemias	Urine organic acids Plasma acylcarnitine profile Molecular testing
Lactic acidosis with ketonuria	Pyruvate carboxylase deficiency (severe) Glycogen storage disease I	Urine organic acids Plasma amino acids Molecular testing
Lactic acidosis, without ketonuria	Pyruvate carboxylase deficiency (mild) Pyruvate dehydrogenase deficiency Mitochondrial dysfunction Hypoxia or hypoperfusion	Urine organic acid analysis Molecular testing
Hyperammonemia, moderate–severe	Urea cycle disorders Organic acidemias Transient hyperammonemia of newborn HHH syndrome Lysinuric protein intolerance	Plasma amino acids Plasma acylcarnitine profile Urine organic acids Molecular testing
Hyperammonemia, mild–moderate	Organic acidemias Severe pyruvate carboxylase deficiency Fatty acid oxidation disorders Carnitine disorders Non-fasting sample	Urine organic acids Plasma amino acids Plasma acylcarnitine profile Plasma carnitine, free and total Molecular testing
Hypoglycemia	Fatty acid oxidation disorders Carnitine disorders Glycogen storage diseases Hyperinsulinism	Urine organic acids Plasma acylcarnitine profile Plasma carnitine, free and total Molecular testing
Seizures	Non-ketotic hyperglycinemia Sulfite oxidase deficiency Molybdenum cofactor deficiency Pyridoxal phosphate sensitive encephalopathy Serine deficiency disorder GLUT-1 deficiency	Plasma amino acids CSF amino acids Urine sulfite (dipstick) Blood and CSF glucose Molecular testing
Liver disease	Galactosemia Disorders of bile acid synthesis	Galactose-1-phosphate (RBC) GALT enzyme assay (RBC) Molecular testing
Cataracts	Galactosemia, mitochondrial dysfunction	Galactose and galactose-1-phosphate. GALT enzyme assay, urine organic acids Molecular testing
Neutropenia	Barth syndrome, glycogen storage disease 1 b, organic acidemias, abnormalities of folate and B12 metabolism	Urine organic acids, plasma total homocysteine, plasma amino acids Molecular testing
Cardiomyopathy, arrhythmia	Long chain fatty acid oxidation disorders, carnitine disorders, Barth syndrome, mitochondrial dysfunction	Plasma acylcarnitine profile Plasma carnitine, free and total Urine organic acids Molecular testing

BOX 18.2 RED, SCALY BABY – LABORATORY EVALUATION

- Gram stain (if infection suspected)
- Fungal smear (if infection suspected)
- Tzanck smear (if infection suspected)
- Appropriate cultures (e.g., nasopharynx/rectum for viruses or bacteria)
- Chest radiograph (may reveal absence thymic shadow in neonate with SCID)
- CBC, platelets
- Quantitative immunoglobulins
- Isohemagglutinins
- Liver function tests
- Electrolytes

- Plasma zinc
- Biotinidase
- RPR
- HIV
- Sweat chloride
- Serum amino/urine organic acids
- Skin fibroblast enzyme analysis
- Trichogram
- Skin biopsy
- T-cell receptor excision circles (TREC)
- T/B-cell functional/quantitative assays (by immunologist)
- DNA analysis for specific disorders

should be performed if infection is suspected. A chest radiograph may be useful to evaluate the thymic shadow, which may be absent in neonates with SCID. A CBC showing lymphopenia in a neonate can suggest a primary immunodeficiency. IgG levels, if obtained during the first months of life, are reflective of maternal values. These may, however, be useful in infants over 6 months of age. Liver function tests may be

indicated in primary or secondary nutritional disease, such as cystic fibrosis. In the latter, one would expect elevations of the transaminases and severely decreased serum albumin. Serum amino and urine organic acids are necessary to screen for suspected cases of primary metabolic diseases, such as the aminoacidurias or biotin deficiencies. A biotinidase level can be obtained if biotin deficiency is suspected. Skin biopsy

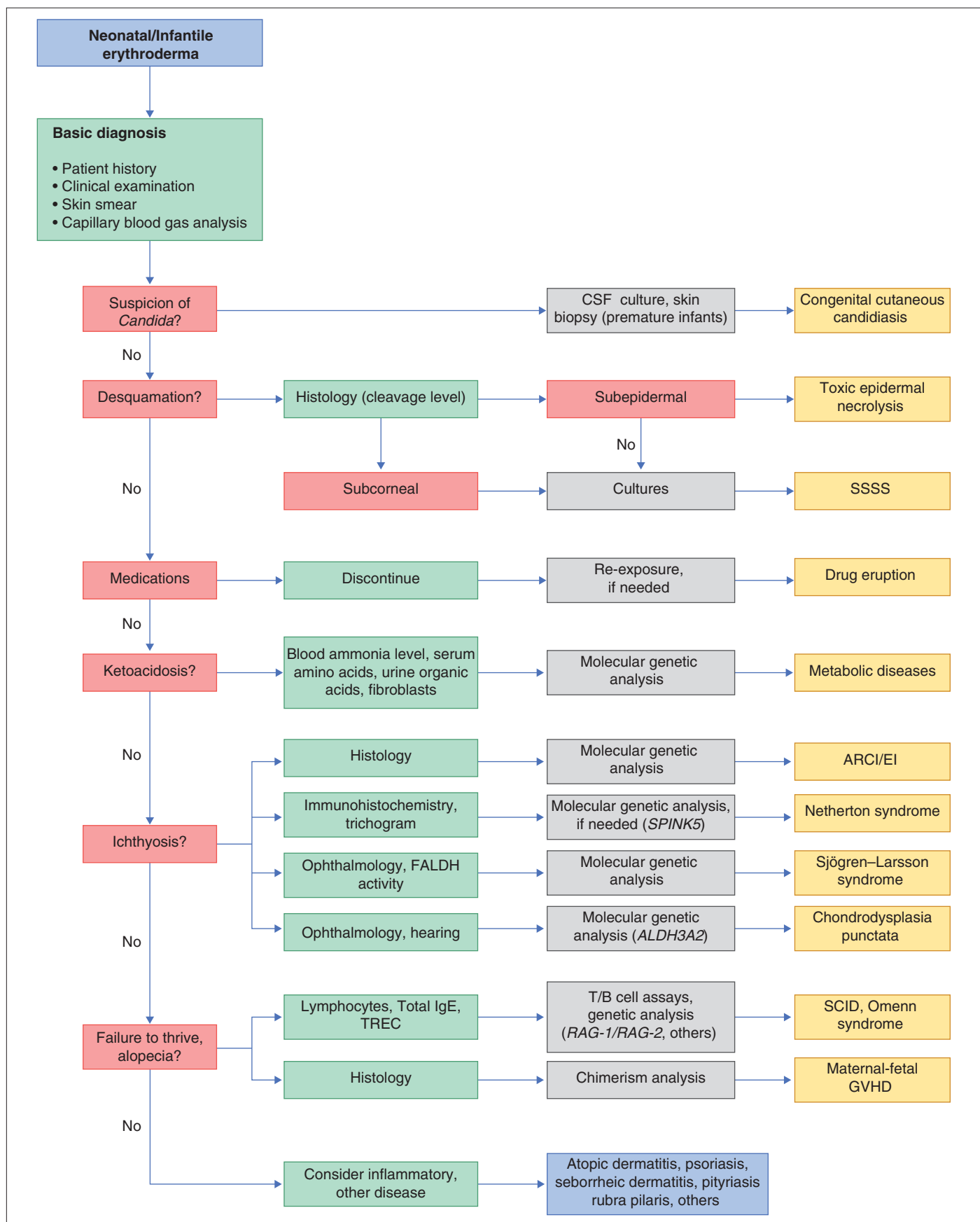


Figure 18.15 A diagnostic algorithm for neonatal/infantile erythroderma. (Modified from Ott H, Hütten M, Baron JM, et al. Neonatal and infantile erythrodermas. *J Dtsch Dermatol Ges* 2008; 6:1070–1086.)

TABLE 18.4 Evaluation and management of disorders

Diagnosis	Usual onset	Clinical features	Associated features	Management
Inflammatory disorders				
Atopic dermatitis	Birth–6 months	Pruritus, xerosis, scaling, and erythema	Skin biopsy: acanthosis, spongiosis	Emollients Topical corticosteroids
Seborrheic dermatitis	Birth–1 month	Greasy scale: scalp, face, body Erythema of body folds and diaper region	Skin biopsy shows features of mild dermatitis and is generally nonspecific	Routine cleansing; occasionally mild topical corticosteroids for short courses
Psoriasis	Birth–adulthood	Mild or thick scale over the scalp and involving diaper areas as well as the abdomen. Periumbilical involvement is typical	Skin biopsy often shows features of chronic dermatitis; spongiotic pustules may rarely be seen	Emollients, low-potency corticosteroids, coal tar/ petrolatum
Diffuse mastocytosis	Birth–2 months	Absence of scale Flushing Blistering Positive Darier's sign	Skin biopsy: dense dermal infiltrate of mast cells. Some infants may show severe syncope, diarrhea, or shock	Prevention of degranulation is important Counseling regarding direct mast cell degranulators should be offered Oral antihistamines (both H1 and H2)
Infectious diseases				
Staphylococcal scalded skin syndrome	Birth–5 years	Diffuse cutaneous erythema followed by superficial desquamation. Mucous membranes are spared	Skin culture of nasopharynx, rectum, or pustule should grow <i>S. aureus</i> Skin biopsy shows superficial epidermal split	Appropriate antibiotics Superficial wound care
<i>Candida</i>	Birth or neonatal	Generalized erythema, papules, scaling, pustules, diffuse erythema	KOH examinations of scraping should be positive Cervical culture for yeast Skin biopsy should show typical fungal elements	Topical therapy for limited disease Systemic antifungal therapy for invasive/disseminated disease
Herpes simplex	Birth or later	Grouped vesicles on erythematous base over presenting part: erosions, scaling, erythema (intrauterine variant)	Tzanck smears showing multiple nucleated giant cells; skin biopsy will show intraepidermal vesicles with ballooning degeneration of keratinocytes Viral culture should be diagnostic Direct fluorescent antibody of scrapings may also be done	Appropriate antiviral therapy
Congenital syphilis	Birth or 6–8 weeks	Bullae, erythema, scaling, eroded papules and plaques over anogenital areas	Dark field examination of mucous membrane lesions: spirochetes specific serology positive	Appropriate antibiotic therapy
Genodermatoses				
Ichthyosis	Birth or later	Diffuse scale, bullae with hyperkeratosis, patterned hyperkeratosis (depending on particular disorder)	Skin biopsy showing epidermolysis with (EI)/ K1,10 genes; retinal changes (Sjögren–Larsson syndrome); bone radiographs showing epiphyseal stippling (chondrodysplasia punctata)	Supportive, emollients, hydration

can be useful for direct histopathologic examination of representative lesions, and fibroblast culture can help in definitive diagnosis of several metabolic diseases.⁴ Lastly, specific molecular testing for genodermatoses, immunodeficiencies, or metabolic diseases is available as discussed above. Consultation with appropriate specialists may be necessary to decide which of these tests are best pursued.

When an infant presents with erythroderma, immediate attention to fluid and electrolytes is paramount. For example, infants with ichthyosis can develop life-threatening hypernatremic dehydration. Infectious complications, primarily

bacterial or fungal, must also be considered. These infants need a warm, humid environment to minimize their metabolic demands. Topical therapy consisting of bland emollients such as petrolatum or Aquaphor® is helpful in minimizing transepidermal water loss and may decrease potential infectious complications.¹⁰²

A summary of the evaluation and management of many of the disorders is found in Table 18.4.

KEY REFERENCES

4. Leclerc-Mercier S, Bodemer C, Bourdon-Lanoy E, et al. Early skin biopsy is helpful for the diagnosis and management of neonatal and infantile erythrodermas. *J Cutan Pathol* 2010;37:249–55.
6. Ott H, Hütten M, Baron JM, et al. Neonatal and infantile erythrodermas. *J Dtsch Dermatol Ges* 2008;6:1070–86.
13. Fraitag S, Bodemer C. Neonatal erythroderma. *Curr Opin Pediatr* 2010;22:438–44.
18. Koga H, Kokubo T, Akaishi M, et al. Neonatal onset diffuse cutaneous mastocytosis: a case report and review of the literature. *Pediatr Dermatol* 2011;28:542–6.
22. Marquez L, Levy ML, Munoz F, et al. A report of three cases and review of intrauterine herpes simplex virus infection. *Pediatr Infect Dis J* 2011;30:153–7.
45. Puck JM. Laboratory technology for population-based screening for severe combined immunodeficiency in neonates: The winner is T-cell receptor excision circles. *J Allergy Clin Immunol* 2012;129:607–16.
69. Al-Herz W, Nanda A. Skin manifestations in primary immunodeficient children. *Pediatr Dermatol* 2011;28:494–501.
72. Schimke LE, Sawalle-Belohradsky J, Roesler J, et al. Diagnostic approach to the hyper-IgE syndromes: Immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. *J Allergy Clin Immunol* 2010;126:611–17.
88. Cook P, Walker V. Investigation of the child with an acute metabolic disorder. *J Clin Pathol* 2011;64:181–91.
100. Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Available at: <http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders>.

REFERENCES

- Bonifazi E, Meneghini CL. Atopic dermatitis in the first six months of life. *Acta Dermatol Venereol* 1989;144:20–2.
- Chu EY, Freeman AF, Jing H, et al. Cutaneous manifestations of DOCK8 deficiency syndrome. *Arch Dermatol* 2012;148:79–84.
- Freeman AF, Holland SM. Clinical manifestations of hyper IgE syndromes. *Dis Markers* 2010;29:123–30.
- Leclerc-Mercier S, Bodemer C, Bourdon-Lanoy E, et al. Early skin biopsy is helpful for the diagnosis and management of neonatal and infantile erythrodermas. *J Cutan Pathol* 2010;37:249–55.
- Janniger CK, Schwartz RA, Musumeci ML, et al. Infantile psoriasis. *Cutis* 2005;76:173–7.
- Ott H, Hütten M, Baron JM, et al. Neonatal and infantile erythrodermas. *J Dtsch Dermatol Ges* 2008;6:1070–86.
- Ivker RA, Grim-Jorgensen CM, Vega VK, et al. Infantile generalized pustular psoriasis associated with lytic lesions of the bone. *Pediatr Dermatol* 1993;10:277–82.
- Abou-Samra T, Constantin J-M, Amarger S, et al. Generalized pustular psoriasis complicated by acute respiratory distress syndrome. *Br J Dermatol* 2004;150:353–6.
- Farber EM, Mullen RH, Jacobs AH, et al. Infantile psoriasis: A follow-up study. *Pediatr Dermatol* 1986;3:237–43.
- Chao PH, Cheng YW, Chung MY. Generalized pustular psoriasis in a 6-week-old infant. *Pediatr Dermatol* 2009;26:352–4.
- Thomson MA, Moss C. Pityriasis rubra pilaris in a mother and two daughters. *Br J Dermatol* 2007;157(1):202–4.
- Yang CC, Shih IH, Lin WL, et al. Juvenile pityriasis rubra pilaris: report of 28 cases in Taiwan. *J Am Acad Dermatol* 2008;59:943–8.
- Fraitag S, Bodemer C. Neonatal erythroderma. *Curr Opin Pediatr* 2010;22:438–44.
- Stern RS. Exanthematous drug eruptions. *N Engl J Med* 2012;366:2492–501.
- Ersoy S, Paller AS, Mancini AJ. Acute generalized exanthematous pustulosis in children. *Arch Dermatol* 2004;140(9):1172–3.
- Riten K, Shahina Q, Jeannette J, et al. A severe case of acute generalized exanthematous pustulosis (AGEP) in a child after the administration of amoxicillin-clavulanic acid: brief report. *Pediatr Dermatol* 2009;26:623–5.
- Lung D, Clancy C. 'Boiled lobster' rash of acute boric acid toxicity. *Clin Toxicol (Phila)* 2009;47:432.
- Koga H, Kokubo T, Akaishi M, et al. Neonatal onset diffuse cutaneous mastocytosis: a case report and review of the literature. *Pediatr Dermatol* 2011;28:542–6.
- Lohmeier K, Megahed M, Schulte KW, et al. Toxic epidermal necrolysis in a premature infant of 27 weeks' gestational age. *Br J Dermatol* 2005;152:150–1.
- Smolinski KN, Shah SS, Honig PJ, et al. Neonatal cutaneous fungal infections. *Curr Opin Pediatr* 2005;17:486–93.
- Rowan JL, Atkins JT, Levy ML, et al. Invasive fungal dermatitis in the < or 1000-gram neonate. *Pediatrics* 1995;95:682.
- Marquez L, Levy ML, Munoz F, et al. A report of three cases and review of intrauterine herpes simplex virus infection. *Pediatr Infect Dis J* 2011;30:153–7.
- Woods CR. Congenital syphilis – persisting pestilence. *Pediatr Infect Dis J* 2009;28:536–7.
- Oji V, Tadini G, Akiyama M, et al. Revised nomenclature and classification of inherited ichthyoses: results of the first ichthyosis consensus conference in Sorèze, 2009. *J Am Acad Dermatol* 2010;63:607–41.
- Chavanas S, Bodemer C, Rochat A, et al. Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nature Genet* 2000;25:141–2.
- Sprecher E, Chavanas S, DiGiovanna JJ, et al. The spectrum of pathogenic mutations in SPINK5 in 19 families with Netherton syndrome: implications for mutation detection and first case of prenatal diagnosis. *J Invest Dermatol* 2001;117:179–87.
- Fartasch M, Williams ML, Elias PM. Altered lamellar body secretion and stratum corneum membrane structure in Netherton syndrome: differentiation from other infantile erythrodermas and pathogenic implications. *Arch Dermatol* 1999;135:823–32.
- Judge MR, Morgan G, Harper JL. A clinical and immunological study of Netherton's syndrome. *Br J Dermatol* 1994;131:615–21.
- Richard G, Moss C, Traupe H, et al. Ichthyosis and disorders of cornification. In: Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 3rd ed. Edinburgh: Mosby; 2003.
- Alio AM, Bird LM, McClellan SD, et al. Sjögren-Larsson syndrome: a case report and literature review. *Cutis* 2006;78:61–5.
- Davis K, Holden KR, S'aulis D, et al. Novel mutation in Sjögren-Larsson syndrome is associated with divergent neurologic phenotypes. *J Child Neurol* 2013;28:1259–65.
- Kalter DC, Atherton DJ, Clayton PT. X-linked dominant Conradi-Hunermann syndrome presenting as congenital erythroderma. *J Am Acad Dermatol* 1989;21:248–56.
- Corbi MR, Conejo-Mir JS, Linares M, et al. Conradi-Hunermann syndrome with unilateral distribution. *Pediatr Dermatol* 1998;15:299–303.
- Ali L, Ricotti C, Li L, et al. Diffuse erythema and dry scales in a female infant. X-linked dominant Conradi-Hunermann-Happle (CHH) syndrome. *Am J Dermatopathol* 2011;33:316, 31.
- Nazzaro V, Blanchet-Burdon C, Lorette G, et al. Familial occurrence of KID (keratosis, ichthyosis, deafness) syndrome. Case reports of a mother and daughter. *J Am Acad Dermatol* 1990;23:385–8.
- Lenane P, Cammisuli S, Chitayat D, et al. What syndrome is this? KID syndrome (keratitis, ichthyosis, deafness). *Pediatr Dermatol* 2006;23:81.
- Srebnik A, Tur E, Perluk C, et al. Dorfman-Chanarin syndrome: A case report and a review. *J Am Acad Dermatol* 1987;17:801–8.
- Happle R, Traupe H, Grobe H, et al. The Tay syndromes (congenital ichthyosis with trichothiodystrophy). *Eur J Pediatr* 1984;141:147–52.
- Galve J, Vicente A, Gonzalez-Ensenat MA, et al. Neonatal erythroderma as a first manifestation of Menkes disease. *Pediatrics* 2012;130:e239–42.
- Executive and Scientific Advisory Boards of the National Foundation for Ectodermal Dysplasia. Scaling skin in the neonate: a clue to the early diagnosis of X-linked hypohidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome). *J Pediatr* 1989;114:600–2.
- Mancini AJ, Lawley LP, Uzel G, et al. X-linked ectodermal dysplasia with immunodeficiency caused by NEMO mutation: early recognition and diagnosis. *Arch Dermatol* 2008;144:342–6.
- Aradhya S, Courtois G, Rajkovic A, et al. Atypical forms of incontinentia pigmenti in male individuals result from mutations of a cytosine tract in exon 10 of NEMO (IKK-gamma). *Am J Hum Genet* 2001;68:765–71.
- Glover MT, Atherton DJ, Levinsky RJ. Syndrome of erythroderma, failure to thrive and diarrhea in infancy: A manifestation of immunodeficiency. *Pediatrics* 1988;81:66–72.
- Fischer A. Severe combined immunodeficiencies (SCID). *Clin Exp Immunol* 2000;122:143–9.
- Puck JM. Laboratory technology for population-based screening for severe combined immunodeficiency in neonates: The winner is T-cell receptor excision circles. *J Allergy Clin Immunol* 2012;129:607–16.
- Hague RA, Rassam S, Morgan G, et al. Early diagnosis of severe combined immunodeficiency syndrome. *Arch Dis Child* 1999;70:260–3.
- Puck JM. The case for newborn screening for severe combined immunodeficiency and related disorders. *Ann NY Acad Sci* 2011;1246:108–17.
- Shearer WT. Screening for severe combined immunodeficiency in newborns. *J Allergy Clin Immunol* 2012;129:619–21.
- Gaspar HB, Cooray S, Gilmour KC, et al. Hematopoietic stem cell gene therapy for adenosine deaminase-deficient severe combined immunodeficiency leads to long-term immunological recovery and metabolic correction. *Sci Transl Med* 2011;3:97.
- Pupo RA, Tying SK, Raimor SS, et al. Omenn's syndrome and related combined immunodeficiency syndromes: diagnostic considerations in infants with persistent erythroderma and failure to thrive. *J Am Acad Dermatol* 1991;25:442–6.
- Katugampola RP, Morgan G, Khetan R, et al. Omenn's syndrome: lessons from a red baby. *Clin Exp Dermatol* 2008;33:425–8.
- Sullivan KE, Mullen CA, Blaese RM, et al. A multi-institutional survey of the Wiskott-Aldrich syndrome. *J Pediatr* 1994;125:876–85.
- Hong R. The DiGeorge anomaly (Catch 22, DiGeorge/velocardiofacial syndrome). *Semin Hematol* 1998;35:282–90.
- Yu S, Graf WD, Shprintzen RJ, et al. Genomic disorders on chromosome 22. *Curr Opin Pediatr* 2012;24:665–71.
- Markert ML, Alexieff MJ, Li J, et al. Complete DiGeorge syndrome: development of rash, lymphadenopathy, and oligoclonal T cells in 5 cases. *J Allergy Clin Immunol* 2004;113:734–41.
- Archer E, Chuan T-Y, Hong R. Severe eczema in a patient with DiGeorge syndrome. *Cutis* 1990;45:455–9.
- Selim MA, Marert ML, Burchette JL, et al. The cutaneous manifestations of atypical incomplete DiGeorge syndrome: a histopathologic and immunohistochemical study. *J Cutan Pathol* 2008;35:380–5.

58. Sullivan KE. The clinical, immunological, and molecular spectrum of chromosome 22q11.2 deletion syndrome and DiGeorge syndrome. *Curr Opin Allergy Clin Immunol* 2004;4:505–12.
59. Dinulos JG, Levy ML. Graft-versus-host disease in children. *Semin Dermatol* 1995;14:66–9.
60. Denianke KS, Frieden IJ, Cowan MJ, et al. Cutaneous manifestations of maternal engraftment in patients with severe combined immunodeficiency: a clinicopathologic study. *Bone Marrow Transplant* 2001;28:227–33.
61. Lerner KG, Kao GF, Storb R, et al. Histopathology of graft-vs-host reaction (GVHR) in human recipients of marrow from HLA matched sibling donors. *Transplant Proc* 1974;6:367–71.
62. Fujinami RS, Nelson JA, Walker L, et al. Sequence homology and immunologic cross-reactivity of human cytomegalovirus with HLA-DR chain: A means for graft rejection and immunosuppression. *J Virol* 1988;62:100–5.
63. Appleton AL, Curtis A, Wilkes J, et al. Differentiation of materno-fetal GVHD from Omenn's syndrome in pre-BMT patients with severe combined immunodeficiency. *Bone Marrow Transplant* 1994;14:157–9.
64. Paller AS, Nelson A, Steffan L. T-lymphocyte subsets in the lesional skin of allogeneic and autologous bone marrow transplant patients. *Arch Dermatol* 1988;124:1795–801.
65. Vogelsa GB, Wolff D, Altomonte V, et al. Treatment of chronic graft-versus-host disease with ultraviolet irradiation and psoralen (PUVA). *Bone Marrow Transplant* 1996;17:1061–7.
66. Grundmann-Kollmann M, Ludwig R, et al. Narrowband UV-B phototherapy in the treatment of cutaneous graft versus host disease. *Transplantation* 2002;75:1631–4.
67. Ochs HD. The Wiskott-Aldrich syndrome. *Semin Hematol* 1998;35:332–45.
68. Thrasher AJ, Kinnon C. The Wiskott-Aldrich syndrome. *Clin Exp Immunol* 2000;120:2.
69. Al-Herz W, Nanda A. Skin manifestations in primary immunodeficient children. *Pediatr Dermatol* 2011;28:494–501.
70. Grimbacher B, Holland SM, Gallin JJ, et al. Hyper-IgE syndrome with recurrent infections – an autosomal dominant multisystem disorder. *N Engl J Med* 1999;340:692–702.
71. Chamlin SL, McCalmont TH, Cunningham BB, et al. Cutaneous manifestations of hyper-IgE syndrome in infants and children. *J Pediatr* 2002;141:572–5.
72. Schimke LF, Sawalle-Belohradsky J, Roesler J, et al. Diagnostic approach to the hyper-IgE syndromes: Immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. *J Allergy Clin Immunol* 2010;126:611–17.
73. Erlewyn-Lajeunesse M. Hyperimmunoglobulin-E syndrome with recurrent infection: a review of current opinion and treatment. *Pediatr Allergy Immunol* 2000;11:133–41.
74. Leung DY, Geha RS. Clinical and immunologic aspects of the hyperimmunoglobulin E syndrome. *Hematol Oncol Clin North Am* 1988;2:81–100.
75. Rosenzweig SD, Holland SM. Phagocyte immunodeficiencies and their infections. *J Allergy Clin Immunol* 2004;113:620–6.
76. Leiding JW, Holland SM. Chronic granulomatous disease. In: *Gene reviews*. Seattle, WA: University of Washington; 2012.
77. Dohil M, Prendiville JS, Crawford RI, et al. Cutaneous manifestations of chronic granulomatous disease: A report of four cases and review of the literature. *J Am Acad Dermatol* 1997;36:899–907.
78. International Chronic Granulomatous Disease Cooperative Study Group. A controlled trial of interferon-gamma to prevent infection in chronic granulomatous disease. *N Engl J Med* 1991;324:509–16.
79. Waldman TA, Wochner RD, Laster L, et al. Allergic gastroenteropathy – a cause of excessive gastrointestinal protein loss. *N Engl J Med* 1967;276:761–9.
80. Jenkins HR, Walker-Smith JA, Atherton DO. Protein-losing enteropathy in atopic dermatitis. *Pediatr Dermatol* 1986;3:125–9.
81. Maloney J, Nowak-Wegrzyn A. Educational clinical case series for pediatric allergy and immunology: allergic proctocolitis, food protein-induced enterocolitis syndrome and allergic eosinophilic gastroenteritis with protein-losing gastroenteropathy as manifestation of non-IgE-mediated cow's milk allergy. *Pediatr Allergy Immunol* 2007;18:360–70.
82. Katz AJ, Twarog FJ, Zeiger RS, et al. Milk sensitive and eosinophilic gastroenteropathy: Similar clinical features with contrasting mechanisms and clinical course. *J Allergy Clin Immunol* 1984;74:72–8.
83. Garganta CL, Smith WE. Metabolic evaluation of the sick neonate. *Semin Perinatol* 2005;29:164–72.
84. Ellaway CJ, Wilcken B, Christodoulou J. Clinical approach to inborn errors of metabolism presenting in the newborn period. *J Pediatr Child Health* 2002;38:511–17.
85. Tabanoglu D, Ersoy-Evans S, Karaduman A. Acrodermatitis Enteropathica-Like eruption in metabolic disorders: Acrodermatitis dysmetabolica is proposed as a better term. *Pediatr Dermatol* 2009;26:150–4.
86. Howard R, Frieden IJ, Crawford D, et al. Methylmalonic aciduria, cobalamin c type, presenting with cutaneous manifestations. *Arch Dermatol* 1997;133:1563–6.
87. Koopman RJ, Happle R. Cutaneous manifestations of methylmalonic aciduria. *Arch Dermatol* 1990;282:272–3.
88. Cook P, Walker V. Investigation of the child with an acute metabolic disorder. *J Clin Pathol* 2011;64:181–91.
89. Roongpisuthipong W, Phanachet P, Roongpisuthipong C, et al. Essential fatty acid deficiency while a patient receiving fat regimen total parenteral nutrition. *BMJ Case Rep* 2012;14 June, doi: 10.1136/bcr.07.2011.4475.
90. Spraker MK, Helmski MA, Elsas LJ. Periorificial dermatitis secondary to dietary deficiency of isoleucine in treated infants with urine disease [abstract]. *J Invest Dermatol* 1986;86:508.
91. Northrup H, Sigman ES, Hebert AA. Exfoliative erythroderma resulting from inadequate intake of branched-chain amino acids in infants with maple syrup urine disease. *Arch Dermatol* 1993;129:384–5.
92. Giacoia GP, Berry GT. Acrodermatitis enteropathica-like syndrome secondary to isoleucine deficiency during treatment of maple syrup urine disease. *Am J Dis Child* 1993;147:954–6.
93. Snyderman SE, Boyer A, Norton PM, et al. The essential aminoacid requirements of infants: isoleucine. *Am J Clin Nutr* 1964;15:313.
94. Theone J, Batshaw M, Spector E. Neonatal citrullinemia: treatment with ketoanalogues of essential aminoacids. *J Pediatr* 1977;90:218–24.
95. Kline JJ, Hug G, Schubert WK, et al. Arginine deficiency syndrome: Its occurrence in carbamoyl phosphate synthetase deficiency. *Am J Dis Child* 1981;135:437–42.
96. Hansen RC, Lemen R, Rersin B. Cystic fibrosis manifesting with acrodermatitis enteropathica-like eruption: Associated with essential fatty acid and zinc deficiencies. *Arch Dermatol* 1983;119:51–5.
97. Darmstadt GL, Schmidt CP, Wechsler DS, et al. Dermatitis as a presenting sign of cystic fibrosis. *Arch Dermatol* 1992;128:1358–64.
98. Zedek D, Morrell DS, Graham M, et al. Acrodermatitis enteropathica-like eruption and failure to thrive as presenting signs of cystic fibrosis. *J Am Acad Dermatol* 2008;58:S5–8.
99. Wenk KS, Higgins KB, Greer KE. Cystic fibrosis presenting with dermatitis. *Arch Dermatol* 2010;146:171–4.
100. Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Available at: <http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders>.
101. Pruszkowski A, Bodemer C, Fraïtag S, et al. Neonatal and infantile erythrodermas. *Arch Dermatol* 2000;136:875–80.
102. Nopper AJ, Horii KA, Sokdeo-Drost S, et al. Topical ointment therapy benefits premature infants. *J Pediatr* 1996;128:660–9.

Disorders of Cornification (Ichthyosis)

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Introduction

The term ‘inherited disorders of cornification’ covers a wide range of genetic conditions with molecular defects that preclude the formation of a normal epidermis. The term is usually considered to include entities divided on morphological grounds into ichthyoses, follicular keratoses, and palmoplantar keratodermas. In addition, many inherited disorders usually considered as ectodermal dysplasias have significant defects in epidermal development or differentiation. Several ichthyotic conditions first manifest in the neonatal period, usually as either collodion baby or scaling erythroderma, or more rarely as a harlequin fetus. In some situations, such as harlequin ichthyosis or Netherton syndrome, associated complications are life-threatening. For most of these conditions, therapy during the neonatal and early infantile periods is supportive (Box 19.1), involving frequent application of bland emollients and monitoring for evidence of infection or fluid and electrolyte imbalance. The use of topical medications with keratolytic agents neonatally and during the first 6 months of life is usually unnecessary and risks significant absorption of potentially toxic substances (e.g., lactic acid, salicylic acid).

General principles of care for affected infants over 6 months of age include prevention of water loss, emolliating and softening of the stratum corneum. This can be achieved with short, 5 minute baths twice daily, and regular application of emollients. Keratolytic agents, such as urea, lactic acid or salicylic acid compounded with emollients, may be used to remove hyperkeratotic scales. These are not always well tolerated in younger children. Topical corticosteroids may be used for concomitant inflammation, however systemic absorption may be increased in patients with poorly formed cornified layers. Antibacterial washes or bleach baths are beneficial in patients with thick scale, who are at increased risk of cutaneous infection, especially from *Staphylococcus* and dermatophytes. In patients with suspected dermatophyte infection, skin scrapings should be taken for confirmation prior to local or systemic treatment with antifungal agents. Affected individuals may have impaired sweating due to occlusion of eccrine ducts and care should be taken to avoid overheating. Consider vitamin D3 supplementation in affected children as they may be at increased risk of developing rickets, due to a reluctance to expose their skin to sunlight.

In the past 15 years, the molecular bases of the great majority of these disorders have been elucidated, thereby laying the groundwork for confirmatory molecular diagnosis and opening up the possibility of genotype–phenotype correlation and DNA-based prenatal diagnosis for several of the devastating forms of ichthyosis. An international consensus for the classification of inherited ichthyosis was published in 2010.¹ Tables 19.1 and 19.2 summarize relevant conditions based on this consensus classification. At present, molecular diagnosis is

not available for all forms of ichthyosis and therapy is not yet gene-based. In addition, access to genetic diagnostics is costly and varies from country to country and among different health insurance providers. A wonderful support group is available for all families with a disorder of cornification, the Foundation for Ichthyosis and Related Skin Types (FIRST; www.firstskinfoundation.org).

Collodion baby

Cutaneous features

Collodion babies are encased at birth in thickened, shiny, variably erythematous skin that resembles cellophane (Fig. 19.1). The collodion baby (Figs 19.1, 19.2) is the phenotype at birth of several ichthyotic disorders, but variable severities of autosomal recessive congenital ichthyoses (ARCI, non-syndromic) are the eventual phenotype in most patients.² Others (syndromic forms) include Sjögren–Larsson syndrome, Conradi–Hünemann syndrome, trichothiodystrophy, and neonatal Gaucher disease.³ In 5–6% of collodion babies, normal-appearing skin replaces the collodion membrane, and these babies have the mildest form of ARCI, termed *spontaneously healing, self-healing, or self-improving* collodion baby.⁴

Extracutaneous features

Despite the thickening of the stratum corneum, the collodion membrane is actually a poor barrier, which can result in excessive transcutaneous fluid and electrolyte loss with resultant hypernatremic dehydration,^{5,6} increased metabolic requirements, and temperature instability owing to increased evaporative cooling. Collodion babies are often premature, and the combined skin disorder and prematurity further increase the risk of complications. In addition, numerous cutaneous fissures may be present which, together with the poor skin barrier, increase the risk of the skin being a site of entry for bacteria and subsequent sepsis. Infection may also be difficult to diagnose owing to the intrinsic temperature instability and fluid imbalances associated with the underlying skin condition. Aspiration of squamous material in the amniotic fluid may lead to neonatal pneumonia.⁷ In addition, the thickening of the skin may restrict movement, making sucking, eye closure, and rarely respiration, difficult.

Etiology and pathogenesis

The underlying basis for collodion babies is varied, reflecting the different forms of ichthyosis that present as collodion babies, and these are discussed below. The most common cause is mutations in transglutaminase 1 (*TGM1*). The self-healing collodion baby phenotype was first shown to be due to mutations in *TGM1*.⁸ In two affected siblings, increased hydrostatic

BOX 19.1 PRINCIPLES OF CARE OF THE COLLODION BABY

Intervention	Reason
Careful fluid and electrolyte balance	Increased TEWL
Humidity controlled environment	Increased TEWL
Temperature controlled environment	Diminished ability to control temperature
Regular bland emollients	Diminished barrier function
Avoid potentially toxic topical medications (e.g., steroids, TIMs, urea, lactic acid)	Diminished barrier function
Prevent infection	Diminished barrier function
Good eye care	Keratitis from prolonged ectropion

TEWL, transepidermal water loss; TIM, topical immunomodulator.

BOX 19.2 EVENTUAL OUTCOMES OF NEONATAL COLLODION BABY PHENOTYPE**COMMON**

- ARCI – Congenital ichthyosiform erythroderma
- ARCI – Lamellar ichthyosis
- ARCI – Self-healing collodion baby

UNCOMMON

- Neutral lipid storage disease with ichthyosis
- Loricrin keratoderma
- Gaucher disease, type II
- Trichothiodystrophy syndromes
- Sjögren–Larsson syndrome
- Conradi–Hünemann syndrome
- ARCI – Harlequin ichthyosis

ARCI, autosomal recessive congenital ichthyosis.



Figure 19.1 Shiny collodion membrane of a 1-day-old collodion baby. Note the eclabium and tightened skin of the hands.



Figure 19.2 One week after birth, this collodion baby with congenital ichthyosiform erythroderma is showing desquamation of scale. Despite the severity of the early phenotype, this infant had very mild congenital ichthyosiform erythroderma at 6 months of age. (From Paller AS. Ichthyosis in the neonate. In: Dyall-Smith D, Marks R, eds. *Dermatology at the millennium: Overview of past achievements, current knowledge and future trends*. London: Parthenon Publishing Group; 1998, with permission.)

pressure significantly reduced the activity of the mutant enzyme, suggesting that this pressure both traps water molecules and locks the mutated enzyme in an inactive *trans* conformation in utero. After birth, these water molecules are removed and the enzyme is predicted to isomerize back to a partially active *cis* form, explaining the dramatic improvement of this skin condition.⁸

Subsequent publications have shown that the ‘self-healing’ variant can reflect underlying mutations in *ALOX12B* or *ALOXE3*, in addition to *TGM1*.⁹

Differential diagnosis

Several conditions can result in the collodion baby phenotype (Box 19.2). Occasionally, severe cases can be confused with harlequin ichthyosis.

Treatment and care

Collodion babies should be placed in high-humidity environments to increase hydration, and bland emollients should be applied (see Box 19.1). Electrolytes should be monitored,⁵ as should fluid intake and output. The membrane usually sloughs during the first month of life (Fig. 19.2). The use of topical keratolytic agents should be avoided in view of the increased potential for toxicity resulting from absorption through the compromised permeability barrier.⁵

Ichthyosis vulgaris**Cutaneous features**

Ichthyosis vulgaris is one of the most common genetic disorders of skin, occurring in approximately 1 in 250 individuals, based on a survey of healthy English schoolchildren.¹⁰ In contrast to other forms of ichthyosis, ichthyosis vulgaris does not manifest during the neonatal period. The condition usually appears after 3 months of age as fine, light-colored scales that are larger and coarser on the lower extremities. Palmoplantar markings are accentuated (hyperlinearity).

Extracutaneous features

There is an association in some cases with atopic asthma and rhinitis in later life, and ichthyosis vulgaris is associated with a strong risk for atopic dermatitis.

TABLE 19.1
Inherited ichthyoses – syndromic

Disorder	Previous name	MIM #	Inh	Cutaneous findings	Extracutaneous findings	Gene defect(s)	Protein(s)	Class of protein/ function
X-linked ichthyosis syndromes								
RXLI (recessive X-linked ichthyosis) syndromic presentation		308100	XR	Large, dark scales Sparing of body folds	Prolongation of labor Cryptorchidism Corneal opacities, asymptomatic	STS Larger deletions with contiguous gene defects	Steroid sulfatase	Enzyme
IFAP syndrome (ichthyosis- follicularis-atrichia- photophobia)		398205	XR	Spiny follicular ichthyosis Nail dystrophy Alopecia	Photophobia Psychomotor delay Short stature	MBTPS2	Membrane-bound transcription factor peptidase, site 2	Enzyme
Conradi-Hünermann- Happle syndrome (CDPX2)	X-linked chondro- dysplasia punctata (Conradi- Hünermann syndrome)	302960	XD	Striated ichthyosiform hyperkeratosis Follicular atrophy/derma Alopecia	Cataracts Frontal bossing Short proximal limbs	EBP	Emopamil-binding protein	Enzyme involved in cholesterol biosynthesis
CHILD syndrome		308050	XD	Unilateral ichthyosiform erythroderma	Chondrodysplasia punctata Cataracts Limb reduction defects Asymmetric organ hypoplasia	NSDHL	3- β -hydroxysteroid- Δ^8,Δ^7 -isomerase	Enzyme involved in cholesterol biosynthesis
Autosomal ichthyosis syndromes with prominent hair abnormalities								
NS (Netherton syndrome)		256500	AR	Erythroderma in infancy Ichthyosis linearis circumflexa Alopecia	Atopic diathesis Food allergies Structural hair defects (trichorrhexis invaginata) Growth delay	SPINK5	LETKI	Serine protease inhibitor
IHS (ichthyosis hypotrichosis syndrome)		610765	AR	Adherent plate-like scale Hypohidrosis Hypotrichosis	Photophobia Pinguiculum	ST14	Serine protease 14	Enzyme
IHSC syndrome (ichthyosis- hypotrichosis- sclerosing cholangitis)		607626	AR	Fine thin scale Hypotrichosis with coarse thick hair	Sclerosing cholangitis Congenital paucity of bile ducts	CLDN1	Claudin 1	Membrane protein involved in tight junctions
TTD (trichothiodystrophy)		601675	AR	May have collodion membrane Can vary from mild scaling to marked adherent plaques	Photosensitivity Brittle hair with 'tiger tail' pattern Decreased fertility Short stature Susceptibility to infection	ERCC2, XPD ERCC3, XPB GTF2H5, TTDA	Xeroderma pigmentosum group D protein Xeroderma pigmentosum group B protein	DNA repair enzymes also involved in regulation of transcription
TTD (not associated with congenital ichthyosis)		234050	AR	Delayed onset Fine scale	Non-photosensitive Brittle hair Short stature Decreased fertility	C7orf11, (TTDN1)	M-phase-specific PLK1-interacting protein, (TTD non- photosensitive 1 protein)	Protein function not fully characterized
Autosomal ichthyosis syndromes with fatal disease course								
Gaucher syndrome, type 2		230900	AR	Collodion baby, mild scaling later	Hepatosplenomegaly retroflexion of the head, strabismus, dysphagia, choking spells, hypertonicity Death usually occurs in the first year	GBA	Acid β -glucosidase	Enzyme

Continued

TABLE 19.1 Inherited ichthyoses – syndromic (Continued)

Disorder	Previous name	MIM #	Inh	Cutaneous findings	Extracutaneous findings	Gene defect(s)	Protein(s)	Class of protein/function
Multiple sulfatase deficiency		272200	AR	Mild scale	Mental retardation Mucopolysaccharidosis Metachromatic leukodystrophy Death within first year of life	SUMF1	Sulfatase-modifying factor-1	Modifier of sulfatase enzyme activity
CEDNIK syndrome (cerebral dysgenesis-neuropathy-ichthyosis-palmoplantar keratoderma)		609528	AR	Coarse plate-like white scale Fine, sparse hair	Sensorineural deafness Cerebral dysgenesis Neuropathy Microcephaly Neurogenic muscle atrophy Optic nerve atrophy Cachexia Lethal within first decade	SNAP29	Synaptosomal-associated protein, 29kDA	Membrane trafficking
ARC syndrome (arthrogryposis-renal dysfunction-cholestasis)		208085	AR	Fine scale	Arthrogryposis Intrahepatic bile duct hypoplasia with cholestasis Renal tubular degeneration Metabolic acidosis Abnormal platelet function Death within first year of life	VPS33B	Vacuolar protein sorting-associated protein 33B	Sorting intracellular molecules
Autosomal ichthyosis syndromes with other associated signs								
SLS (Sjögren-Larsson syndrome)		270200	AR	Fine lamellar scale	Di- or tetraplegia Retinal glistering white dots	ALDH3A2	Long-chain-aldehyde dehydrogenase	Enzyme
RS (Refsum syndrome) (HMSN4; hereditary motor sensory neuropathy type 4)	Refsum disease	266500	AR	Late onset, fine scale	Retinitis pigmentosa Cardiac failure	PAHX or PHYH PEX7	Phytanoyl-CoA hydroxylase Peroxin-7	Enzymes involved in phytanic acid metabolism
KID syndrome (keratitis-ichthyosis-deafness syndrome)	KID; includes HID syndrome	242150 602540	AD	Verrucous plaques Stippled pattern of keratoderma	Keratitis Sensorineural deafness	GJB2 (GJB6)	Connexin 26	Gap junction protein
Neutral lipid storage disease with ichthyosis	Chanarin-Dorfman syndrome (also termed NCIE2)	275630	AR	Fine scales with occasional background erythema	Myopathy Hepatosplenomegaly	ABHD5	CGI-58	Enzyme, a member of the esterase/lipase/thioesterase subfamily
IPS (ichthyosis prematurity syndrome)		608649	AR	White caseous scale, attenuated on scalp and eyebrows Follicular keratosis	Atopic manifestations	SLC27A4	Long-chain fatty acid transport protein 4	Transport and activation of fatty acids
CHIME syndrome		280000	AR	Ichthyotic erythema Occasionally migratory plaques	Colobomas Conductive hearing loss Mental retardation	NK	NK	NK
MEDNIK syndrome (mental retardation-enteropathy-deafness-neuropathy-ichthyosis-keratoderma)		Not on OMIM	AR	Rough, thickened skin	Congenital sensorineural deafness Psychomotor and growth retardation Chronic diarrhea	API51	Adapter-related protein complex 1 sigma-1A subunit	Endocytosis and Golgi processing

Table
19.2
Inherited ichthyoses – non-syndromic

Disorder	Previous name	MIM #	Inh	Cutaneous findings	Extracutaneous findings	Gene defect(s)	Protein(s)	Class of protein/function
Common ichthyoses								
IV (ichthyosis vulgaris)		146700	AD (autosomal semidominant)	Fine, white scale Accentuated palmoplantar markings Large, dark scales Sparing of body folds	Strong association with atopic manifestations Prolongation of labor Cryptorchidism Corneal opacities, asymptomatic	FLG	Filaggrin	Structural component of stratum corneum
RXLI (recessive X-linked ichthyosis) (non-syndromic presentation)		308100	XR			STS	Steroid sulfatase	Enzyme
Autosomal recessive congenital ichthyosis (ARCI)								
MAJOR TYPES								
HI (harlequin ichthyosis)		242500	AR	Rigid plates Severe erythema Hypohidrosis Scarring alopecia	Ectropion Eclabium Contractures Failure to thrive Short stature	ABCA12	ATP-binding cassette, subfamily a, member 12	ABC transporter
LI (lamellar ichthyosis)		242300 601277 604777	AR	Large adherent plates Hypohidrosis	Ectropion Eclabium Short stature if severe	TGM1, ABCA12, PNPLA1, LIPN	Transglutaminase 1, ABCA12 transporter, PNPLA1, Lipase N	Enzyme involved in crosslinking of stratum corneum ABC lipid transporter Glycerophospholipid synthesis or remodeling
CIE (congenital ichthyosiform erythroderma)		242100	AR	Fine white scales Background erythema Hypohidrosis Mild PPK White nails	Failure to thrive Short stature if severe Occasional neurologic	TGM1, ALOX12B, ALOXE3, ABCA12, CYP4F22, NIPAL4	Transglutaminase 1, Arachidonate lipooxygenases, cytochrome P450 enzyme, ichthyin, ABCA12 transporter	Comified envelope crosslinking Lipoxygenase/hepoxilin pathway Lipid transporter
MINOR VARIANTS								
SHCB (self-healing collodion baby)		242300	AR	Collodion baby at birth, not subsequent ichthyotic phenotype	None	TGM1, ALOX12B, ALOXE3	Keratinocyte transglutaminase 1	Enzyme involved in crosslinking of stratum corneum
Acral SHCB (self-healing collodion baby)		242300	AR	Acral collodion membranes that heal	None	TGM1	Transglutaminase 1	Comified envelope crosslinking
BSI (bathing suit ichthyosis)		242300	AR	Collodion membrane at birth, extremities heal	None	TGM1	Transglutaminase 1	Comified envelope crosslinking

Continued

Table 19.2 Inherited ichthyoses – non-syndromic (Continued)

Disorder	Previous name	MIM #	Inh	Cutaneous findings	Extracutaneous findings	Gene defect(s)	Protein(s)	Class of protein/function
Keratinopathic ichthyosis (KPI)								
MAJOR TYPES								
EI (epidermolytic ichthyosis)	BCIE/EH	113800	AD, rarely AR	Widespread skin blistering in neonates Warty hyperkeratosis Mild flexural hyperkeratosis Adherent fine scale Pruritus	Growth failure if severe	KRT1, KRT10	Keratins 1 and 10	Cytoskeleton structural protein
SEI (superficial EI)	Ichthyosis bullosa of Siemens	146800	AD		None	KRT2E	Keratin 2	Cytoskeleton structural protein in suprabasal layer
MINOR VARIANTS								
AEI (annular epidermolytic ichthyosis)		607602	AD	Intermittent annular, polycyclic erythematous scaly plaques		KRT1, KRT10	Keratins 1 and 10	Cytoskeleton structural protein
ICM (ichthyosis Curth-Macklin)	Ichthyosis hystrix	146590 146600	AD	Spiky hyperkeratosis	None	KRT1	Keratin 1	Cytoskeleton structural protein
Epidermolytic epidermal nevi		Not in OMIM	Somatic mutations			KRT1, KRT10	Keratins 1 and 10	Cytoskeleton structural protein
Other forms								
LK (loricrin keratoderma)		604117	AD	Collodion baby Mild, fine, white scale Diffuse PPK	None	LOR	Loricrin	Abnormal intranuclear granules
EKV (erythrokeratoderma variabilis)		133200	AD	Transient, migratory erythematous patches Hyperkeratosis Diffuse PPK	None	GJB3, GJB4	Connexins 31, 30.3	Gap junction proteins
PSD (peeling skin disease)		270300	AR		None	CDSN, TGM5	Corneodesmin, Transglutaminase 5	Corneocyte adhesion Epidermal crosslinking Structural protein
CRIE (congenital reticular ichthyosiform erythroderma)		609165	AD (isolated cases)		None	KRT10	Keratin	
KLICK (keratosis linearis-ichthyosis congenita-keratoderma)		Not in OMIM	AR	Linear keratosis in skin folds Sclerosing PPK	None	POMP	Proteasome maturation protein	Molecular chaperone

Etiology and pathogenesis

Mutations in the filaggrin gene (*FLG*) have now clearly been shown to underlie ichthyosis vulgaris, leading to decreased or absent expression of filaggrin.¹¹ These mutations are semi-dominant; heterozygotes exhibit a very mild phenotype with incomplete penetrance, whereas homozygotes or compound heterozygotes show much more severe disease. The mutations show a combined allele frequency of ~4% in Caucasian populations, explaining the high incidence of ichthyosis vulgaris. *FLG* gene mutations are now well established as the highest genetic risk for atopic dermatitis.

Differential diagnosis

In affected boys, ichthyosis vulgaris in the young infant may need to be distinguished from X-linked recessive ichthyosis (see below).

Treatment and care

In the neonatal period no specific care is necessary. Good skin care with regular emollients and the avoidance of irritants such as detergents is advisable, as these infants tend to have lifelong dry skin and a high incidence of atopic dermatitis.¹⁰

Recessive X-linked ichthyosis

Cutaneous features

Recessive X-linked ichthyosis (RXLI) is a disorder that affects 1:6000–1:2000 males. The ichthyosis manifests by 3 months of age in 84% of patients, although only 17% show evidence of exaggerated neonatal desquamation and peeling at birth. Extensor surfaces, the preauricular areas, and the sides of the neck are most severely affected by the large, dark, adherent scales (Fig. 19.3).

Extracutaneous features

RXLI is regarded as syndromic when accompanied by associated manifestations and non-syndromic when ichthyosis is isolated.¹ The absence of steroid sulfatase activity during fetal life also leads to increased fetal production of DHEAS (dehydroepiandrosterone sulfate) and decreased placental estrogen production, which may delay the progression of parturition.



Figure 19.3 Diffuse scaling of the trunk and extremities is seen in this 2-week-old infant with X-linked ichthyosis.

Rarely, affected boys have hypogonadism with undescended testes, hypoplasia of the penis and scrotum, and/or failure of normal sexual maturation. The development of testicular cancer has been described in one patient without undescended testes. Approximately 10% of affected boys have a contiguous gene deletion syndrome, a larger deletion which encompasses genes that are contiguous with the steroid sulfatase gene on the terminal short arm of the X chromosome. Deletion of surrounding genes results in mental retardation, hypogonadism, and anosmia (Kallmann syndrome), or a bone dysplasia characterized radiographically by stippled epiphyses (X-linked recessive chondrodysplasia punctata).

Etiology and pathogenesis

X-linked ichthyosis results from mutations of the *STS* gene encoding steroid sulfatase (arylsulfatase C), particularly deletions (90% of patients). In a study assessing the clinical and molecular features in 28 patients with Kallmann syndrome 1, submicroscopic deletions were found at Xp22.3 in four contiguous genes, *VCXA*, *STS*, *KAL1*, and *OAI*.¹²

Differential diagnosis

Recessive X-linked ichthyosis (RXLI) in the neonate is not associated with collodion membrane and is therefore distinguishable from other ichthyotic disorders associated with collodion membranes and early skin thickening. Ichthyosis vulgaris is an important differential diagnosis in older male infants and can be distinguished by fluorescent in situ hybridization (FISH) and other genetic analyses. Patients with RXLI, who additionally have a concomitant *FLG* mutation, have a more severe manifestation of their RXLI. Babies with the rare autosomal recessive disorder, multiple sulfatase deficiency, show scaling typical of RXLI and decreased steroid sulfatase due to a global deficiency of sulfatases. Affected patients also show neurologic abnormalities characteristic of metachromatic leukodystrophy, and features of storage diseases because of the deficiency of several additional sulfatases.

Treatment and care

In the neonatal period, no specific care is necessary, but patients will generally need lifelong skin care advice and appropriate emollients. RXLI may be detected prenatally. The most common scenario for this is in pregnancies not known to be at risk with an abnormal 'triple screen' test that detects decreased maternal estriol levels. RXLI may then be confirmed by FISH, *STS* (steroid sulfatase), and DHEAS for deletions and/or the demonstration of decreased placental sulfatase activity in amniotic fluid cells and increased DHEAS levels in amniotic fluid.

Inherited syndromic ichthyoses – X-linked

ICHTHYOSIS FOLLICULARIS, ALOPECIA, AND PHOTOPHOBIA (IFAP SYNDROME)

Cutaneous features

Patients are born with thickening of the skin, including the palms and soles, with generalized prominent follicular keratosis and mild erythema.^{13,14} The clinical findings have been described as a 'nutmeg grater'.¹⁵ The scalp is hairless, and severe photophobia is noted from birth. The nails may be dystrophic, and

follicular pustules may be present. Biopsies show a hyperkeratotic stratum corneum with a thinned dermis. The hair follicles are atrophic and shortened, with abnormal localization of the bulbs to the deep portion of the dermis, rather than a subcutaneous location. There are no normal hair shafts, and sebaceous glands are absent. It is possible that at least two other forms exist in addition to this classic form.^{16,17}

Extracutaneous features

Some patients have had short stature, psychomotor delay, and/or seizures. Ocular changes including corneal ulceration, greatly reduced visual acuity,¹⁸ and cataract¹⁹ have been reported.

Etiology and pathogenesis

IFAP syndrome is an X-linked disorder caused by functional deficiency of membrane-bound transcription factor protease, site 2 (MBTPS2).²⁰ This results in disturbed differentiation of epidermal structures evoking the triad of ichthyosis follicularis, atrichia and photophobia.²⁰ Female carriers may have linear involvement.²¹ An autosomal recessive form has also been described.

Differential diagnosis

The constellation of clinical signs should make the diagnosis apparent.

Treatment and care

Systemic retinoids have been used in children as young as 3 years, with reported improvement.²²

CONRADI-HÜNERMANN-HAPPLE SYNDROME (X-LINKED CHONDRODYSPLASIA PUNCTATA)

Cutaneous features

Most cases of chondrodysplasia punctata are the X-linked dominant Conradi-Hünemann-Happle form. Affected neonates are usually female, because the disorder is considered lethal to male fetuses. However, Conradi syndrome has been described in a few male patients with and without Klinefelter syndrome.²³ At birth, patients most commonly have patterned erythroderma with overlying thin to thick psoriasiform scale (Fig. 19.4). In severe cases, generalized ichthyosiform erythroderma with thick scale is seen at birth,²⁴ and later shows typical patterning along Blaschko's lines with scale desquamation. Involvement may be predominantly unilateral. With advancing age the ichthyosiform erythroderma and stippling improve, leaving finer scaling without underlying erythema and follicular atrophoderma. Cicatricial alopecia occurs as scalp scaling resolves. Psychotropism may be seen (see 'CHILD syndrome', below).

Extracutaneous features

Extracutaneous features include limb reduction, typically asymmetric, and facies with frontal bossing, saddle nose, and malar hypoplasia. Asymmetric, focal stippled calcifications of the epiphyseal regions are common in childhood but typically disappear in adulthood. Bone defects normally begin soon after birth and during childhood as punctate calcifications, as a result of abnormal calcium deposition during endochondral bone formation. They typically appear in the epiphyses of the long bones, but may also develop in the scapulae, clavicles, sternum,

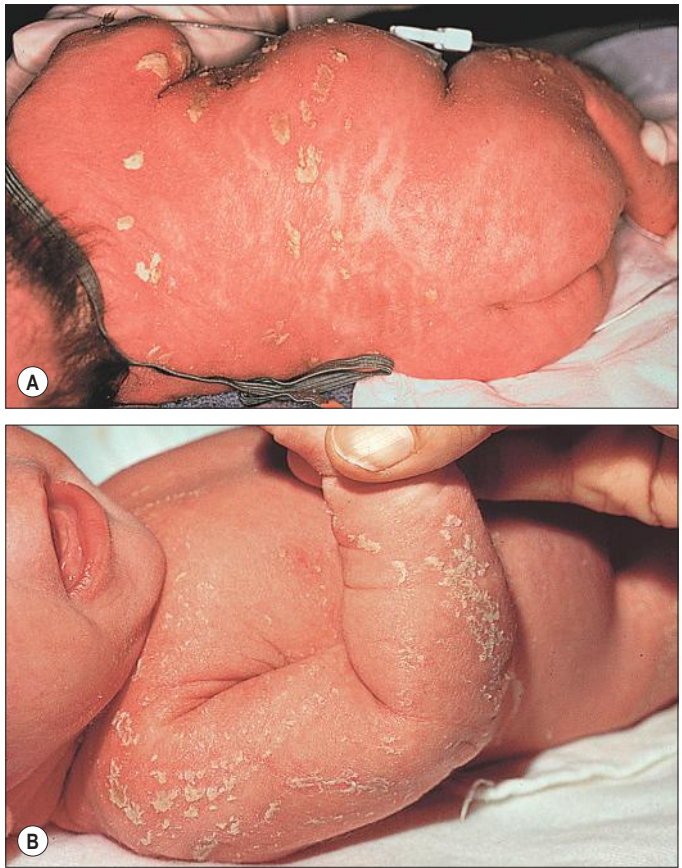


Figure 19.4 Conradi-Hünemann syndrome. (A) Thick, psoriasiform scaling overlying erythema in a 1-month-old girl with the syndrome and chondrodysplasia punctata. As the scaling desquamated, the underlying erythema along Blaschko's lines became more apparent. (B) The pattern of scale along Blaschko's lines is more evident in this neonate with Conradi-Hünemann syndrome. (From Paller AS. *Ichthyosis in the neonate*. In: Dyll-Smith D, Marks R, eds. *Dermatology at the millennium: Overview of past achievements, current knowledge and future trends*. London: Parthenon Publishing Group; 1998, with permission.)

ribs, and spinal column. These lesions usually disappear during adulthood.²⁵

Cataracts usually develop later during childhood, but may be present at birth.²³

Etiology and pathogenesis

The underlying molecular basis is mutations in emopamil binding protein (3 β -hydroxysteroid- Δ 8, Δ 7-isomerase), which is involved in cholesterol synthesis (see below).²⁶ Chondrodysplasia punctata can be inherited in both autosomal and X-linked fashion, and may also be the result of an environmental insult, particularly fetal exposure to warfarin.²⁴

Differential diagnosis

The differential diagnosis usually includes two other forms of chondrodysplasia punctata: autosomal recessive rhizomelic chondrodysplasia punctata,²⁴ and X-linked recessive chondrodysplasia punctata with steroid sulfatase deficiency.²⁷ The rhizomelic form is also associated with multiple peroxisomal defects. The ichthyosis occurs in approximately one-third of patients and is poorly described. Affected patients have developmental retardation and tend to die as infants. The X-linked

recessive form of chondrodysplasia punctata occurs as a contiguous gene deletion syndrome of Xp, not at the site of Conradi syndrome. The ichthyosis is consistent with recessive X-linked ichthyosis, but stippled epiphyses are associated. Affected infants are deficient in steroid sulfatase activity, and have no peroxisome defects.

Treatment and care

There is no specific care for the neonate with Conradi syndrome.

CHILD SYNDROME

Cutaneous features

The term 'CHILD syndrome' is an acronym for 'congenital hemidysplasia with ichthyosiform nevus and limb defects'. The condition occurs almost exclusively in girls, and is presumed to be lethal in affected males. The only case in a boy is thought to represent early postzygotic mosaicism.²⁸ The inflammatory ichthyosiform skin lesion of CHILD syndrome may be present at birth or develop during the first few months of life.^{28,29} It is characterized by yellow, waxy scaling and is strikingly unilateral, generally with a sharp demarcation at the ventral and dorsal midline regions (Fig. 19.5). Streaks of inflammation and scaling can also follow Blaschko's lines, with involvement of the apparently unaffected side of the body. Similarly, streaks of normal skin may be interspersed within the area of the CHILD nevus. With increasing age, the skin lesions may improve or clear spontaneously, but thickened erythematous plaques in intertriginous areas tend to persist and be the most severely affected sites (psychotropism).³⁰ The skin lesions of CHILD syndrome nevus can occur without any other abnormalities, but the occurrence of all features of CHILD syndrome in a sibling of a patient with

only the CHILD nevus suggests variable expressivity within the spectrum of CHILD syndrome.³¹

Extracutaneous features

A variable degree of ipsilateral skeletal hypoplasia is an important feature of CHILD syndrome. As with the skin changes, unilaterality is not absolute and slight changes may be present on the contralateral side. Punctate epiphyseal calcifications may be demonstrable by X-ray, but tend to disappear after the first few years of life. Cardiovascular and renal abnormalities are the major visceral problems in CHILD syndrome, although anomalies of other viscera have been described.²⁹

Etiology and pathogenesis

Biopsy of skin lesions shows epidermal acanthosis with marked parakeratosis alternating with orthokeratosis. Basophilic ghost cells of the granular layer are common. The papillary dermis is often filled with histiocytes showing foamy cytoplasm, resulting in the characteristic histopathologic pattern of verrucous xanthoma. Patients with CHILD syndrome have mutations in 3 β -hydroxysteroid dehydrogenase, an enzyme in the cholesterol biosynthetic pathway.³²

Differential diagnosis

The nevus of CHILD syndrome needs to be distinguished from inflammatory linear verrucous epidermal nevus and linear psoriasis by the histopathologic features and the constellation of other clinical manifestations, if present. CHILD syndrome shares features with Conradi–Hünemann syndrome (see above), a disorder that results from mutation in another gene within the cholesterol biosynthetic pathway; shared characteristics include the prevalence in girls with a presumed X-linked dominant inheritance pattern, ichthyosiform erythroderma, limb reduction defects, stippled epiphyses, and peroxisomal defects. The unilateral nature of the nevus and limb deformities helps to distinguish these conditions.

Treatment and care

Patients with CHILD syndrome tend to tolerate topical medications poorly, other than bland emollients. However, dramatic improvement has been demonstrated in adults with twice daily application of compounded 2% lovastatin and 2% cholesterol.³³ Orthopedic involvement may be needed to manage the limb hypoplasia, including with a prosthesis or even partial amputation. Multisystem care may include cardiology and renal evaluation as needed.

Inherited syndromic ichthyoses with prominent hair signs

NETHERTON SYNDROME

Cutaneous features

Netherton syndrome should be suspected in the neonate with generalized scaling erythroderma, especially if there is failure to thrive (Fig. 19.6).³⁴ Affected infants are often born prematurely and develop the typical ichthyosiform erythroderma in utero or during the first weeks of life. A collodion baby phenotype is not associated. The classic hair shaft abnormality, trichorrhexis invaginata ('bamboo hairs', 'ball-and-socket deformity'), is thought to result from a defect in keratinization of the internal root sheath. Multiple hairs from different areas should be



Figure 19.5 CHILD syndrome. Sharply demarcated, erythematous ichthyosiform lesions with mostly unilateral distribution and hemidysplasia are characteristic findings. Thickened, yellow-brown scale in a whorled pattern is seen within areas of the CHILD nevus.



Figure 19.6 A 32-day-old infant with failure to thrive, hypernatremic dehydration, and ichthyosiform erythroderma was diagnosed with Netherton syndrome by microscopic examination of one of just a few sparse hairs. Note the sparse hair secondary to trichorrhexis invaginata. The infant died of sepsis at 3 months of age. (Courtesy of Dr Bernice Krafchik, Toronto, Canada.)

examined, as only 20–50% of hairs may be affected. Although trichorrhexis invaginata may be present in the neonatal period, delayed and sparse hair growth at this time, as well as the easy breakage of these hairs, makes demonstration of the hair defect in the neonatal period difficult. Ichthyosis linearis circumflexa, the characteristic skin change associated with Netherton syndrome, is usually not seen before 2 years of age, but occurs eventually in 70% of patients. It manifests episodically, often lasting for a few weeks and then clearing for weeks or months. The ichthyosiform erythroderma, however, frequently improves with age. The atopic diathesis becomes problematic in two-thirds of patients, with the development of pruritic atopic dermatitis, multiple food allergies, and often accompanying urticaria, angioedema, asthma, and/or anaphylaxis.

Extracutaneous features

The failure to thrive is often profound, requiring hospitalization for nutritional support and correction of the hypernatremic dehydration that may be associated. Patients may have diarrhea, and occasionally demonstrate villus atrophy if intestinal biopsy is performed. Most patients have increased levels of IgE, but other laboratory and clinical evidence of immune dysfunction may be present as well. The increased risk of sepsis occurs as a result of both the abnormal skin barrier and the associated immune defects that are only in part owing to malnutrition.

Etiology and pathogenesis

The underlying molecular basis for Netherton syndrome is mutations in *SPINK5*, a serine protease inhibitor.^{35,36} Lymphoepithelial Kazal-type-related inhibitor (LEKTI), a putative serine protease inhibitor, is strongly expressed in differentiated keratinocytes in normal skin. The lamellar granule system

transports and secretes LEKTI earlier than its potential serine protease targets kallikrein 5 and kallikrein 7, thus preventing degradation of desmoglein 1 and premature loss of stratum corneum integrity/cohesion.^{37,38} Deficiency of LEKTI also leads to excessive cleavage of profilaggrin to filaggrin, further affecting differentiation.

Differential diagnosis

Netherton syndrome in the neonatal period must be distinguished from several other disorders with extensive scaling erythroderma, failure to thrive, and increased risk of infection, particularly several immunodeficiency disorders, other ichthyoses, and atopic or psoriasiform erythroderma (see Chapter 18). Skin biopsy sections show subacute or chronic seborrheic or psoriasiform dermatitis with spongiosis.³⁹ The stratum corneum is thin and focally parakeratotic, and the granular layer is reduced. Electron microscopic studies have revealed features in skin biopsy specimens that are specific to Netherton syndrome, particularly the premature secretion of lamellar body contents, foci of electron-dense material separating lipid membranes, and disturbed maturation of lamellar membrane structures. Immunohistochemical staining to LEKTI, the protein product of *SPINK5*, is also possible and with increasing availability will become a highly useful diagnostic investigation,⁴⁰ but is currently not widely available.

Treatment and care

Treatment of Netherton syndrome is extremely difficult. Despite their pruritic, erythematous skin, patients tend to respond poorly to topical steroids, although some have improved after topical application of calcineurin inhibitors or calcipotriol. The poor cutaneous barrier of patients with Netherton syndrome may result in significant absorption of topically applied agents. For example, high blood levels of tacrolimus have been found following topical application for the associated dermatitis.⁴¹ The application of keratolytic agents or administration of systemic retinoids often worsens the severity of the disorder, and their use is inappropriate during the neonatal period. Most patients prefer to use bland, thick emollients as the only therapy throughout life.

ICHTHYOSIS HYPOTRICHOSIS SCLEROSING CHOLANGITIS SYNDROME

Cutaneous features

Collodion membrane and absent hair may be presenting features at birth. Patients display varying degrees of ichthyosis, jaundice, scarring alopecia and hypotrichosis, not necessarily all obvious from birth.

Extracutaneous features

Congenital paucity of the bile ducts may be a primary feature leading to hepatomegaly, cholestasis and hepatic fibrosis, without fatty infiltration.⁴² Hepatic involvement varies from transient cholestasis to liver failure. Mild psychomotor delay and bilateral anterior uveal synechiae have been described along with oligodontia, hypodontia and dysplastic enamel.^{42,43}

Etiology and pathogenesis

This is a rare autosomal recessive disorder caused by homozygous mutations affecting the *CLDN1* gene coding for the tight

junction component claudin-1, leading to lack of expression of *CLDN1* in skin and liver.⁴⁴

Differential diagnosis

Consider this syndrome in any child born with collodion membrane, alopecia and neonatal cholestasis.

Treatment and care

Treatment should follow recommendations for collodion babies. In addition, the hepatic manifestations should be evaluated and managed by specialists.

TRICOTHODYSTROPHY (IBIDS SYNDROME (TAY SYNDROME), PIBIDS SYNDROME, SIBIDS SYNDROME)

Cutaneous features

Three autosomal recessive subsets of trichothiodystrophy (TTD) are associated with ichthyosis: IBIDS (ichthyosis with brittle hair, intellectual impairment, decreased fertility, and short stature; Tay syndrome), PIBIDS (IBIDS with photosensitivity), and SIBIDS (IBIDS with osteosclerosis). Of these, PIBIDS is the most common, comprising approximately 50% of cases of TTD. Neonates with TTD and ichthyosis are usually born with a collodion membrane. The severity of the ichthyosis after the membrane is shed is variable, ranging from a mild to a severe lamellar ichthyosis phenotype. In trichothiodystrophy the hair has a 10–50% reduction in sulfur content, leading to brittle hair that shows transverse fractures (trichoschisis), a decreased cuticular layer with twisting, and a nodular appearance that mimics trichorrhexis nodosa. Polarizing microscopy shows a ‘tiger-tail’ pattern of alternating light and dark bands consistent with the alternating content of sulfur in the hair. Examination of hairs at birth by polarizing microscopy may not reveal the tiger-tail pattern, and repeated examinations may be necessary later in the first months of life.⁴⁵

Extracutaneous features

Several other clinical features may be associated, including low birthweight, nail dystrophy, increased susceptibility to infection, neutropenia, hypothyroidism, nystagmus, optic atrophy, cataracts, and hypertonemia.⁴⁶ Not uncommonly, patients die of sepsis during childhood.

Etiology and pathogenesis

Cells from patients with PIBIDS show decreased DNA repair levels similar to those of patients with xeroderma pigmentosum (XP), but the development of skin cancer has not been described. The variable and multiple clinical features of PIBIDS may be due in part to the many genes that can result in this phenotype. TTD syndromes have been shown to be due to phenotype-specific mutations in either *XPB* or *XPD*. These genes encode the helicase subunits of TFIIH, a DNA repair factor that is also required for transcription of class II genes,⁴⁷ so that the brittle hair of PIBIDS syndrome may result from decreased transcription of the genes that encode the sulfur-rich matrix of hair and nails. TFIIH is a complex factor that includes the *XPD* and *XPB* gene products.⁴⁸ Recently, a 75 amino-acid protein, designated p8 or GTF2H5, was identified as the tenth protein in this complex. This peptide appears to be critical in maintaining TFIIH base levels, which are known to be diminished in TTD-A,

where there is an isolated congenital hair defect.⁴⁹ Inactivating mutations in this gene have been shown to cause TTD-A.⁵⁰

Differential diagnosis

In the neonatal period, other causes of collodion membrane need to be excluded. The development of extracutaneous features facilitates the diagnosis.

Treatment and care

Management of the ichthyosis is as usual (see Box 19.1). Prenatal diagnosis of PIBIDS has been performed by DNA repair measurements in amniotic fluid cells, with confirmation by polarizing microscopic analysis of fetal hair.⁵¹

Other inherited syndromic ichthyoses

SJÖGREN–LARSSON SYNDROME

Cutaneous features

This autosomal recessive disorder usually manifests in the neonatal period with slight or moderate widespread ichthyosis,^{52–54} although rarely features may not occur until the infant is older than 6 months. Mild erythema is occasionally present at birth, which clears within months. Only one baby with Sjögren–Larsson syndrome has been reported to have had a collodion membrane at birth. Affected babies usually show thickening of the skin, especially at the umbilicus, neck, and flexural areas, that resembles lichenification. Scaling, if present, is fine and lamellar, so that some neonates have been misdiagnosed as being postmature. Some neonates with Sjögren–Larsson syndrome have had taut, shiny fingers and toes. By 1 year of age the ichthyosis is fully developed, with generalized thickening, lamellar scaling, often a yellowish hue, and relative sparing of the central face, and often the palms and soles. The ichthyosis of Sjögren–Larsson is less scaly and more lichenified in appearance, reminiscent of a mild generalized acanthosis nigricans, and pruritus is typically more prominent than in other forms of ichthyosis (Fig. 19.7). Hair and nails are normal. Histopathologic examination of biopsied skin shows significant hyperkeratosis and papillomatosis, with abnormal lamellar or membranous inclusions.⁵⁵

Extracutaneous features

Most infants with SLS are born preterm.⁵⁶ Mental and motor retardation and spastic diplegia or tetraplegia are the most common extracutaneous features. Many patients have speech abnormalities, seizures, short stature, and kyphosis. Pathognomonic retinal ‘glistening dots’ are not present in all patients. The neurologic disease usually becomes apparent in the first year of life, often by 3 months of age, with failure to reach normal developmental milestones and the onset of spasticity. Phenotypic variability may be seen: in one family three of four siblings had skin findings but none were typical of SLS, and one lacked skin lesions entirely.⁵⁷

Etiology and pathogenesis

Sjögren–Larsson syndrome results from mutations in fatty aldehyde dehydrogenase, a component of fatty alcohol: nicotinamide adenine dinucleotide oxidoreductase (FAO), which converts fatty alcohol to fatty acid.^{54–58} Fatty alcohol is used for the biosynthesis of wax esters, which are largely produced in skin, and of glycerol ether lipids, which are prominent in myelin.



Figure 19.7 Sjögren–Larsson syndrome with flexural lichenification.

There appears to be no genotype–phenotype correlation.⁵⁶ Prenatal diagnosis of Sjögren–Larsson syndrome is possible by measurement of FAO activity in cultured amniocytes or chorionic cells, histologic analysis, and/or analysis of fetal DNA if the gene defect is known.⁵⁹

Differential diagnosis

The pruritus and resemblance to lichenification could be confused with atopic dermatitis. The development of neurological manifestations distinguishes SLS. The ethnic background may provide a useful clue to diagnosis, given the high prevalence in northern Sweden (8.3 in 100 000 persons; elsewhere in Sweden and worldwide the incidence is 0.4 per 100 000).⁵⁶ Diagnosis may be made by demonstrating enzyme deficiency or by mutation analysis of fatty aldehyde dehydrogenase gene (FALDH).

Treatment and care

There are no well-established specific treatments, but rare patients have shown improved behavior and pruritus with 5-lipoxygenase inhibitors.⁶⁰

GAUCHER DISEASE

Cutaneous features

Gaucher disease (β -glucocerebrosidase deficiency) is an autosomal recessive disorder that results from the deficient activity of lysosomal glucocerebrosidase. Several infants with the type II (acute infantile cerebral or acute neuronopathic) form of Gaucher disease have been born with a collodion membrane.^{3,61,62} The enzyme deficiency with resultant abnormalities in glucocerebrosidase degradation appears directly responsible for the abnormal skin of these infants. Glucosylceramide and ceramide are components of the intercellular bilayers in the stratum corneum that participate in skin permeability barrier function, so that the absence of glucocerebrosidase (which increases glucosylceramide and reduces the generation of

ceramide) leads to abnormal skin thickening and increased transepidermal water loss.

Extracutaneous features

Extracutaneous features of type II Gaucher disease include enlargement of the abdomen due to hepatosplenomegaly, and neurologic signs such as retroflexion of the head, strabismus, dysphagia, choking spells, and hypertonicity. Death usually occurs before the age of 1 year. Although patients with type II typically have acute neurologic progression and those with type III have slow progression, some children have been reported with an intermediate phenotype of delayed age of onset, rapid progression of neurologic disease with refractory seizures, and oculomotor abnormalities.⁶³

Etiology and pathogenesis

Gaucher disease type II is caused by mutation in the gene encoding acid β -glucosidase (GBA). Mutations in this gene also cause Gaucher disease type I and type III. Type II is the least common form.⁶⁴

Treatment and care

Management of Gaucher disease type II is palliative, as most children die in the first year.⁶⁵ Knowledge of genotype–phenotype correlation and assessment of biomarkers⁶⁶ may be helpful in delineating severity and counseling parents.

KERATITIS, ICHTHYOSIS, DEAFNESS (KID) SYNDROME

Cutaneous features

The constellation of vascularizing keratitis, ichthyosiform hyperkeratosis, and sensorineural deafness is the characteristic feature of KID syndrome. Patients are usually born with erythematous or erythrokeratodermatous skin that is mildly scaling, although in some the presence of excessive vernix-like material is the presenting finding. Occasionally skin abnormalities are not noted until a few weeks of age.⁶⁷ The characteristic thick, leathery skin with tiny stippled papules develops during the first year of life, particularly during the first 3 months (Fig. 19.8). Well-defined verrucous hyperkeratotic plaques develop in 90% of patients, often localized to the face and limbs. Diffuse palmoplantar hyperkeratosis with a stippled or leathery pattern also occurs in almost all patients. Alopecia occurs overall in 80% of patients, ranging from minimal loss of eyebrows or eyelashes to total scalp alopecia; in 25% of patients the alopecia is congenital. An additional 17% of patients have sparse, fine hair without frank alopecia. The scalp may be markedly thickened in the affected neonate. Nails are dystrophic in the majority of patients. Sweating may be decreased or absent. Biopsy of skin shows nonspecific acanthosis with papillomatosis and basket-weave hyperkeratosis. Hair follicles may be atrophic. Squamous cell carcinoma of the skin and tongue has been described in more than 10% of patients, and may occur during childhood.

Extracutaneous features

The hearing loss is sensorineural, congenital, and can be progressive. It can be detected in the neonate by brainstem-evoked auditory potential testing. Unlike the auditory changes, ophthalmologic features are progressive and most commonly



Figure 19.8 Keratitis-ichthyosis-deafness (KID) syndrome. (A) Characteristic hyperkeratosis, thick leathery skin, and alopecia are evident. (B) Close-up of the leg demonstrates skin furrows and tiny stippled papules commonly seen in KID syndrome. (Courtesy of Marcos Antezana, MD.)

develop in childhood or early adolescence, although photophobia from birth has been described. The keratoconjunctivitis sicca with corneal vascularization leads to pannus formation and markedly decreased visual acuity.⁶⁸ Approximately 45% of patients have recurrent infections, especially bacterial and candidal infections of the skin, auditory canals, and eyes. Some patients have shown evidence of immunodeficiency, with moderate increases in IgE levels, defective chemotaxis, and absent lymphocyte proliferative responses to *Candida albicans*.⁶⁹ Death

from infection during infancy or early childhood has been reported.⁷⁰

Etiology and pathogenesis

Mutations in the *GJB2* gene encoding the gap junction protein connexin 26 are now known to be the cause of KID syndrome in a majority of cases.⁷¹ There does appear to be genetic heterogeneity, however, with mutations also identified in *GJB6*, which encodes connexin 30.⁷² Connexins are the major proteins of gap junctions, which facilitate efficient cell-cell communication between all cells in multicellular organisms. This system facilitates a synchronized cellular response to a variety of intercellular signals by regulating the direct passage of low-molecular-weight metabolites (<1 kDa) and ions between the cytoplasm of adjacent cells.⁷³ The skin and inner ear have a high number of gap junctions, and in the skin they appear to have a role in the coordination of keratinocyte growth and differentiation.⁷⁴ Mutations in these connexins underlie epidermal disease, sensorineural hearing loss, and peripheral neuropathy.^{75,76}

Differential diagnosis

Distinction from Clouston syndrome, another connexin 30 gene disorder (see below), can be difficult.⁷² In both conditions the associated keratoderma has a characteristic 'stippled' quality that is quite distinctive. Detection of deafness is indicative of KID syndrome. Molecular diagnosis is now relatively straightforward, as connexin genes are small and easily screened for mutations.

Treatment and care

Therapy is supportive, but corneal and cochlear implants⁷⁷ have been successfully performed to treat corneal vascularization and the hearing loss, respectively. Oral fluconazole therapy of recalcitrant fungating candidiasis can result in complete resolution and remission for at least a year.⁷⁸

NEUTRAL LIPID STORAGE DISEASE WITH ICHTHYOSIS (CHANARIN-DORFMAN SYNDROME)

Cutaneous features

This autosomal recessive disorder is characterized by the multisystemic accumulation of neutral lipids (triglycerides).⁷⁹ Approximately 65% of affected patients have associated ichthyosis, which is always present at birth as congenital ichthyosiform erythroderma, or occasionally as a collodion membrane.

Extracutaneous features

Hepatomegaly occurs in 46% of patients, although fatty liver may be universal. Liver levels of transaminases are often elevated.^{80,81} Almost 70% of patients have either elevated serum creatine kinase activity or muscle weakness, or both, usually mild and first symptomatic in adulthood. Other features may include ataxia, mental retardation, sensorineural hearing loss, and cataracts.

Etiology and pathogenesis

Sections of skin show accumulation of neutral lipids and these non-membrane-bound cytosolic triacylglycerol droplets are also found in liver, muscle, intestinal mucosa, and neutrophils.

Vacuolated neutrophils are considered the most consistent marker for neutral lipid storage disease. Mutations in the *CGI-58* gene have been found in several families.⁸² The gene product belongs to a large series of proteins most of which are enzymes in the esterase/lipase/thioesterase subfamily. It is widely expressed in skin, lymphocytes, liver, skeletal muscle, and brain.

Differential diagnosis

In the neonate, the ichthyosis may be impossible to distinguish from other CIE phenotypes and possible causes of collodion baby. Diagnosis is usually made by a peripheral blood smear, which shows lipid droplets in granulocytes.⁸³

Treatment and care

Preliminary observations suggest that a low-fat diet, including medium-chain triglycerides, may improve liver function and the skin, especially if begun in early childhood.⁸⁴

ICHTHYOSIS PREMATURETY SYNDROME

Cutaneous features

Ichthyosis prematurity syndrome (IPS) is a distinct form of ichthyosis that is reported primarily in the Norwegian population.⁸⁵ At birth, the skin, particularly on the head and peripheral extremities, is covered by a thick, caseous, desquamating epidermis. The skin changes observed at birth improve within 2 weeks, and after a few months, IPS is characterized by dryness, mild skin stippling (particularly on the distal extremities), a leather-like thickening on the lower back and atopic manifestations, often with hypereosinophilia.⁸⁶

Extracutaneous features

Pregnancies are complicated by polyhydramnios, and ultrasound shows opaque amniotic fluid. The birth is premature, and delivery usually takes place at around 30–32 weeks' gestation. Affected children may suffer from postnatal asphyxia, possibly related to aspiration of amniotic debris.

Etiology and pathogenesis

The pattern on electron microscopy is characterized by membrane aggregations in the upper epidermal cells. Mutations occur in a gene encoding the fatty acid transporter 4 (*SLC27A4*).⁸⁷ *SLC27A4*, expressed in the suprabasal layer of the epidermis, encodes a protein, FATP4, that functions as a fatty acid transporter and an acyl coenzyme A synthetase. Reduced function of this protein most likely leads to disturbance of the intercellular lipid layer of the stratum corneum.

Differential diagnosis

The differential diagnosis in the neonatal period includes collodion membrane and harlequin ichthyosis.

Treatment and care

For general neonatal management principles, see [Box 19.1](#).

CHIME SYNDROME: COLOBOMAS OF THE EYE, HEART DEFECTS, ICHTHYOSIS, MENTAL RETARDATION, EAR DEFECTS

Cutaneous features

The skin is thick and dry at birth. There may be a diffuse, erythematous, pruritic, migratory rash at or shortly after birth



Figure 19.9 CHIME syndrome. Note the migratory erythema in both axillae, and the characteristic thick lips seen in this syndrome.

which becomes increasingly ichthyotic, especially at flexural surfaces, and ultimately resembles lichenification ([Fig. 19.9](#)).⁸⁸ Examination of biopsied skin specimens shows nonspecific changes.⁸⁹ The hair may be fine and sparse, with trichorrhexis nodosa seen on light microscopy.

Extracutaneous features

Affected individuals have a distinctive facies with ocular hypertelorism, brachycephaly, epicanthal folds, macrostomia, and a broadened nasal root. The ear defects can be morphologic, with a cupped appearance and rolled helices, or functional. The colobomas are most commonly retinal, although choroidal colobomas have been described.⁹⁰ Heart defects are common including tetralogy of Fallot, transposition of the great vessels and ventricular septal defect.⁸⁸ Other frequent characteristics include seizures and a wide-based gait. Cleft palate and renal anomalies have been described.

Etiology and pathogenesis

This extremely rare neuroectodermal disorder is thought to be autosomal recessive. Mutations in the *PIGL* gene have recently been described in five previously reported cases.⁹¹

Differential diagnosis

Other ichthyoses with neurologic manifestations should be considered including Sjögren–Larsson syndrome, Netherton syndrome, Refsum disease, KID syndrome and Tay syndrome. The characteristic ocular, cardiac, ear and dysmorphic features help confirm the diagnosis.

Treatment and care

Affected neonates should have ophthalmology, otorhinolaryngology and cardiology assessments.

MEDNIK SYNDROME: MENTAL RETARDATION-ENTEROPATHY-DEAFNESS-NEUROPATHY-ICHTHYOSIS-KERATODERMA

MEDNIK syndrome is a recently described, rare autosomal recessive condition, in a French Canadian population. The phenotype is a result of a mutation in the *APIS1* gene, which is expressed in the skin and spinal cord. Cutaneous features are similar to erythrodermatitis variabilis (see below). Extracutaneous features

include severe psychomotor retardation, peripheral neuropathy, sensorineural hearing loss and severe congenital diarrhea.⁹²

Inherited ichthyoses – non-syndromic

AUTOSOMAL RECESSIVE CONGENITAL ICHTHYOSIS (ARCI)

Within months of shedding their collodion membranes, the majority of babies with ARCI declare their clinical phenotype along a spectrum of manifestations ranging from generalized erythroderma with finer scale (congenital ichthyosiform erythroderma or CIE) to larger, lamellar scaling and variable underlying erythroderma (lamellar ichthyosis or LI). Neonates with harlequin ichthyosis present with and ultimately have a more severe phenotype than the rest of the ARCI group (see below). Because the underlying genetic basis within the ARCI spectrum is varied, without strong genotype-phenotype correlation with respect to scale morphology or erythroderma, other than for harlequin ichthyosis, the etiology/pathogenesis of this group of disorders is discussed together.

HARLEQUIN ICHTHYOSIS

Cutaneous features

Harlequin ichthyosis (HI) is a rare autosomal recessive disorder in which the neonate is born with a thick covering of armor-like scales, severe ectropion and eclabium, and underdeveloped nose and ears (Fig. 19.10). It is likely that the dysmorphic features observed in harlequin ichthyosis are at least in part secondary to restricted fetal movement; this condition has been termed ‘fetal deformation sequence’ (FADS).⁹³ Occasionally infants with HI present with a thick vernix-like coating. Those who survive the perinatal period go on to express a severe and very scaly erythroderma.¹

Extracutaneous features

There is high neonatal mortality due to respiratory complications, infections through the defective skin barrier, and dehydration.

Differential diagnosis

Severe forms of collodion baby may cause confusion but the diagnosis of harlequin ichthyosis is usually straightforward.

Treatment and care

In general, harlequin babies require vigorous supportive therapy, including a humid environment, the aggressive use of emollients, and careful monitoring of fluid and electrolyte needs. Survival past the neonatal period is uncommon, but reported. Most affected infants have complications, such as systemic infection through fissured skin, difficulties with feeding and respiration, and distal gangrene. Therapy with retinoids may improve the clinical appearance, but the condition at best evolves into a severe generalized ichthyosiform erythroderma phenotype.^{94–98} Harlequin ichthyosis is the only ichthyotic condition that may justify the use of systemic retinoid therapy during the newborn period. Treatment with retinoids, first undertaken in 1985, encourages shedding of the grossly thickened skin.^{99,100} A recent review of 45 cases reported an overall survival rate of 56%, ages 10 months to 25 years.¹⁰⁰ Death usually occurred in the first three months from sepsis and/or respiratory failure. The administration of systemic retinoids should generally be considered in infants who have survived the first few weeks with intensive nursing support, although a possible exception is in infants with particularly thick areas of plate-like scale causing digital constriction, in which the early use of retinoids may cause faster desquamation, potentially helping to avoid digital gangrene. The parental decision to use retinoids should be made with the knowledge that the resultant ichthyotic condition is severe and associated with a poor quality

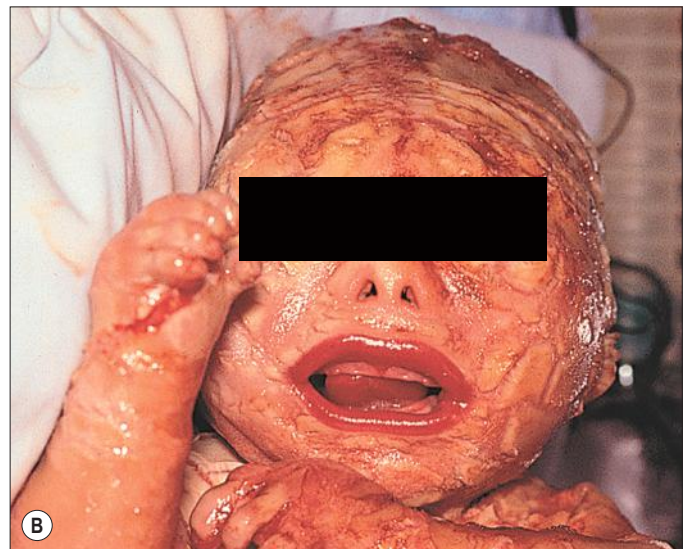
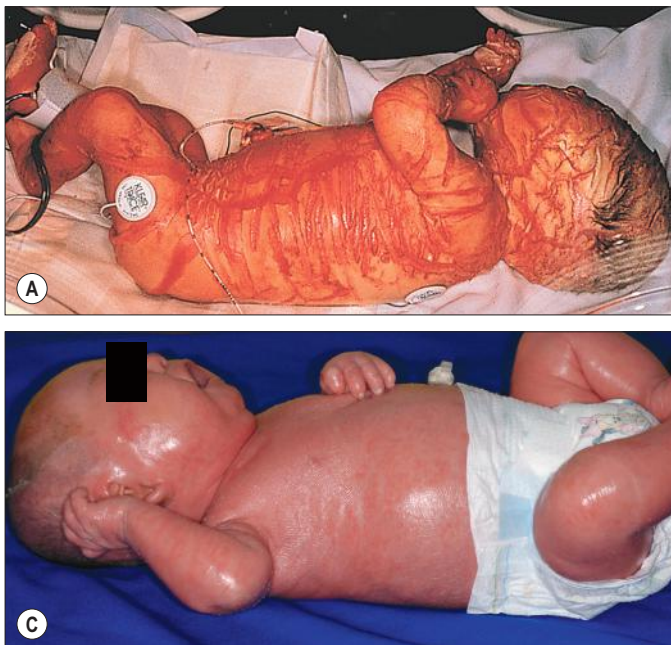


Figure 19.10 (A) Thick armor-like scaling and fissures in a neonate with harlequin ichthyosis. (B) Note the severe ectropion, eclabium, and digital contractures. (C) Harlequin ichthyosis after desquamation. (B: Courtesy of Dr Sylvia Suarez.)

of life. The recovery of lipid secretion after gene correction of *ABCA12* in cultured cells raises hope for future therapeutic approaches.¹⁰¹

LAMELLAR ICHTHYOSIS PHENOTYPE OF ARCI

Cutaneous features

Lamellar ichthyosis (LI) is a phenotype of ARCI, although an autosomal dominant form has been described.¹⁰² Most affected babies have a collodion membrane at birth (see above). After the first months, infants show large and plate-like scales that are often hyperpigmented, particularly in patients with darker skin.¹⁰³ Underlying erythroderma is minimal, but ectropion and alopecia may be severe. Biopsies from patients with LI have massive thickening of the stratum corneum, mild acanthosis, and a normal granular layer. The epidermis in LI may show papillomatosis with regular psoriasiform blunting and broadening of the rete ridges. Bathing suit ichthyosis, a rare minor variant, is characterized by scaling in a bathing suit pattern confined to the trunk.¹⁰⁴

Extracutaneous features

Neonates and infants with severe forms of ARCI can face similar problems to those with Harlequin ichthyosis (discussed above). Care needs to be taken to carefully monitor and take corrective action for variations in body temperature, fluid balance and caloric intake. In later childhood, exposure keratitis can result from prolonged ectropion.

Differential diagnosis

Lamellar ichthyosis can be difficult to distinguish from nonbulbous congenital ichthyosiform erythroderma in the neonatal period.

Treatment and care

In the neonatal period, general supportive measures are appropriate (see Box 19.1). In older children and adults more potent topical keratolytic preparations and oral retinoids may be appropriate, but these should be avoided in infancy.

CONGENITAL ICHTHYOSIFORM ERYTHRODERMA PHENOTYPE OF ARCI

Cutaneous features

Patients with congenital ichthyosiform erythroderma (CIE) also usually present as collodion babies (Fig. 19.11). Underlying erythroderma is common, and the scales tend to be finer and lighter in color than those of infants with lamellar ichthyosis. Alopecia and ectropion may be associated.¹⁰³

Extracutaneous features

Not uncommonly, patients with CIE have associated neurologic abnormalities, and the CIE phenotype may be part of syndromic ichthyosis, such as neutral lipid storage disease (Chanarin–Dorfman syndrome). These patients have failure to thrive and short stature, if severe.

Differential diagnosis

Because of the associated neurological abnormalities and the potential to respond to dietary tailoring, it is important to

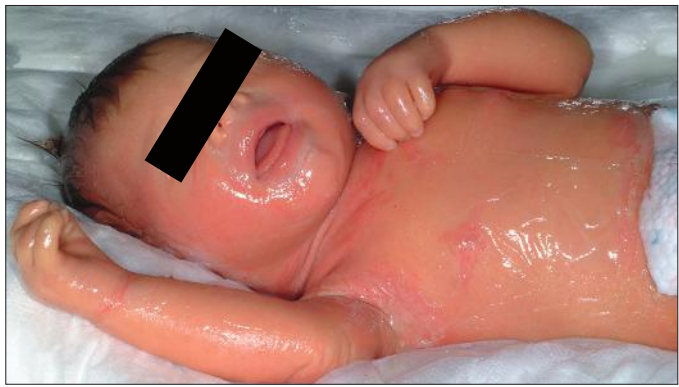


Figure 19.11 Collodion baby with ARCI of the congenital ichthyosiform erythroderma (CIE) phenotype due to an *ALOX12B* mutation.

exclude Chanarin–Dorfman syndrome (see below). However, this is a very uncommon cause of the CIE phenotype.

Treatment and care

See Box 19.1 for general principles of care in the neonatal period.

ETIOLOGY AND PATHOGENESIS OF THE ARCI GROUP

The genetic basis for ARCI is heterogeneous, and seven genes have been found to have mutations that lead to ARCI (see Table 19.1).^{105,106} The gene most commonly altered in ARCI (32% of patients in one series¹⁰⁵) is transglutaminase 1 (*TGM1*),¹⁰⁷ encoding an enzyme that is involved in cornified envelope formation by crosslinking precursor proteins such as involucrin. Other genes mutated in ARCI encode proteins of the tepoxalin pathway, including *NIPAL4* (ichthyin, 16% of ARCI); *ALOX12B* (12(R)-lipoxygenase, 12%); *CYP4F22* (a cytochrome P450 enzyme of the 12(R)-lipoxygenase pathway, 8%); *ALOXE3* (lipoxygenase-3, 5%), as well as the lipid transporter *ABCA12*.¹⁰⁵ Besides their disruption of stratum corneum lipid synthesis, these enzymes (or receptors) within the lipoxygenase pathway may also disrupt the processing of profilaggrin to filaggrin.¹⁰⁸ To date, all babies with harlequin ichthyosis have had mutations in the lipid transporter *ABCA12*.^{11,101,109} Missense mutations in *ABCA12* may result in a milder phenotype that shows a collodion membrane at birth and which progresses into LI or CIE, often with palmoplantar keratoderma (PPK).¹¹ The integrity of the stratum corneum barrier is largely due to corneocytes embedded in intracellular lipid lamellae. These extracellular lipid lamellae are in turn formed from intracellular granules. Absence of *ABCA12* prevents the transfer of lipids into lamellar granules, leading to histologic demonstration of lipid accumulation within corneocytes and absence of normal lamellar granules,¹² poor barrier and secondary clinical changes.¹¹⁰ A seventh and most recently identified cause of ARCI is mutations in *PNPLA1*, which contribute to the epidermal lipid barrier.¹⁰⁶ Within the ARCI spectrum is also a late onset form with lamellar scaling due to mutations in *LIPN*, encoding lipase N.¹¹¹ Prenatal diagnosis by molecular analysis of fetal DNA, obtained by chorionic villus sampling, is a preferred method of prenatal diagnosis of ARCI, once the molecular defect is known.¹¹²

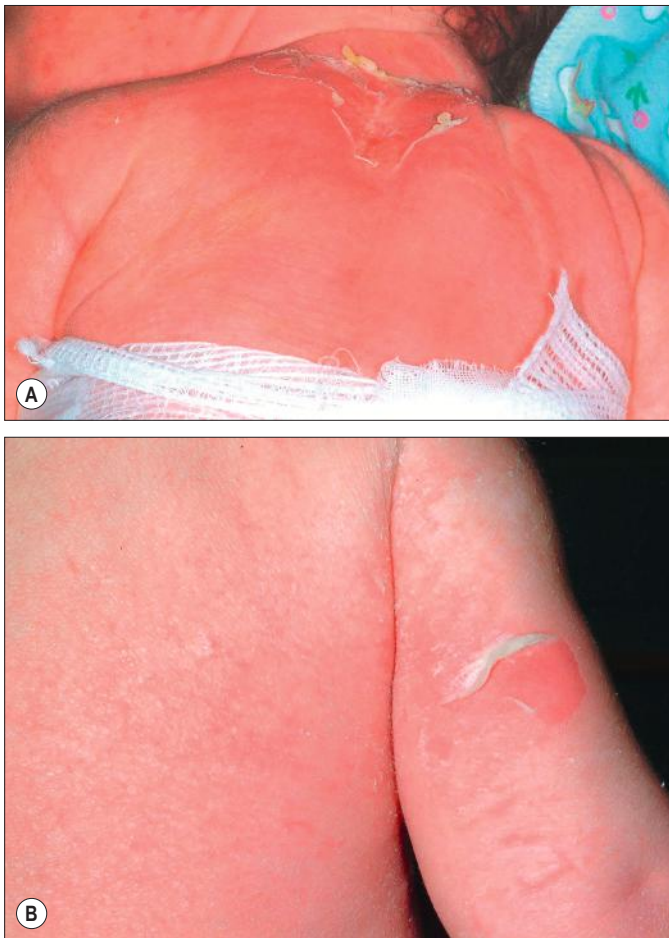


Figure 19.12 Epidermolytic ichthyosis. (A) Blistering in a neonate often occurs at the site of trauma. (B) In this infant, erythema and fine scale are more prominent. Scaling becomes more verrucous as the patient becomes older, especially in intertriginous areas and overlying joints.

Keratinopathic ichthyosis

In this group of disorders, mutations in keratin genes lead to fragile skin and blistering with compensatory thickening of overlying skin.

EPIDERMOLYTIC ICHTHYOSIS (EI)

Previously called 'epidermolytic hyperkeratosis'.

Cutaneous features

This autosomal dominant disorder manifests in the neonate as widespread areas of denuded skin with only subtle skin thickening and/or scaling (Fig. 19.12). Confusion with other blistering disorders in the neonate is common, particularly epidermolysis bullosa, and secondary cutaneous bacterial infection caused by *Staphylococcus aureus* often occurs. As patients age, the scaling becomes more verrucous, with large dark scales, particularly at intertriginous sites, and the propensity towards blistering tends to decrease. Annular EI is a subtype characterized by annular polycyclic erythematous plaques over the proximal extremities and trunk.¹¹³

Extracutaneous features

In the neonatal period, infants with EI risk dehydration, electrolyte imbalance, and infection; however, most babies do well and death rarely occurs in neonates.

Etiology and pathogenesis

The gene defects of EI involve abnormalities of keratins 1 or 10,^{114,115} the major differentiation-specific keratins of the upper epidermis. These mutations cause the formation of defective keratin filaments, which are functionally responsible for the tonofilament clumping and blistering of this disorder. Prenatal diagnosis has been performed at 20–24 weeks' gestation by fetal skin biopsy, based on the abnormal clumping of keratin filaments,¹¹⁶ but also by molecular analysis of keratin 10 in an affected family.¹¹⁷

Differential diagnosis

Distinction from epidermolysis bullosa is important in the neonatal period. The principles of care at this stage remain the same, but accurate diagnosis is important in order to properly inform and counsel parents. The histologic appearance of lesional skin confirms the diagnosis, showing vacuolization of the granular and upper spinous layers. Hyperkeratosis, acanthosis, and papillomatosis are variable, but the granular layer is thickened. On electron microscopy the tonofilaments are seen to be clumped in the lower epidermal layers and form perinuclear shells in the granular cell and upper spinous layers.

Treatment and care

The neonate should be managed according to the same broad principles as outlined in Box 19.1, but with additional specific precautions on skin handling of neonates with fragile skin directed by a detailed nursing protocol.

ICHTHYOSIS CURTH-MACKLIN

Cutaneous features

Ichthyosis Curth–Macklin (ICM) (previously ichthyosis hystrix), is a rare autosomal dominant ichthyotic disorder characterized by plaques of spiny hyperkeratosis. The extent of involvement varies from patchy to generalized and severe. In patients with patchy involvement, the distribution is not along the lines of Blaschko. Usually, the face, palms, and soles are not affected, but involvement of the penis and scrotum has been described. Affected infants tend to show cutaneous changes within the first weeks of life, with subsequent progression of involvement, although onset during childhood has been described in some patients. Erythroderma may be present at birth, but disappears with time.

Extracutaneous features

None.

Etiology and pathogenesis

Microscopic examination of skin biopsy specimens shows orthokeratosis, papillomatosis, and acanthosis of the granular and upper spinous layers, with perinuclear vacuolization. Keratinocytes may have two nuclei. Ultrastructural examination shows concentric shells of tonofibrils that encase the nuclei with perinuclear vacuoles, lamellar body abnormalities, and

binuclear keratinocytes.¹¹⁸ In two families, the ICM phenotype has been attributed to mutations in keratin 1.^{119,120} The condition is genetically heterogeneous; in other families linkage to the keratin gene clusters has been excluded.¹²¹

Differential diagnosis

ICM can be confused with epidermolytic ichthyosis. The lack of erythroderma, blistering, and typical ultrastructural characteristics distinguish these conditions. Epidermal nevi, although they may resemble ICM both clinically and histologically, are distinguishable by their distribution along the lines of Blaschko.

Treatment and care

Neonatal care is outlined in Box 19.1. In older children, keratolytics and oral retinoids may be of value.

Miscellaneous forms of ichthyosis

PEELING SKIN DISEASE

Cutaneous features

This rare autosomal recessive condition is characterized by spontaneous superficial peeling of skin, sometimes accompanied by pruritus and occasionally by erythema or vesiculation. Skin involvement is usually generalized, but the palms, soles, face, and scalp may be unaffected. The Nikolsky sign tends to be positive, and a skin biopsy often shows psoriasiform epidermal changes and shedding of the stratum corneum just above the granular layer. Pruritus and atopy may be associated.

Extracutaneous features

Transient eosinophilia and elevation of IgE levels, with food allergies is commonly associated.

Etiology and pathogenesis

Peeling skin disease is caused by homozygous nonsense mutations in *CDSN* leading to complete loss of corneodesmosin, an epidermal adhesion molecule.¹²² Acral peeling skin syndrome was previously thought to be a variant of PSD but is now known to be a distinct disease caused by a mutation in transglutaminase 5 (*TGM5*).¹²²

Differential diagnosis

The clinical appearance may initially be confused with staphylococcal scalded skin syndrome but the duration and distribution should make the distinction clear.

Treatment and care

General principles of care apply (see Box 19.1).

ERYTHROKERATODERMA VARIABILIS (EKV)

Cutaneous features

This autosomal dominant disorder manifests as two types of skin change. Some patients have migratory patches of erythema, which are often targetoid or circinate and last for days to months. With time, the lesions become more fixed, erythematous, and hyperkeratotic (Fig. 19.13). In other patients, the disorder manifests as sharply demarcated, fixed hyperkeratotic plaques. Both types of lesion may be seen in the same patient.



Figure 19.13 Erythrokeratoderma variabilis. Sharply demarcated erythematous hyperkeratotic plaques on the trunk of an affected child.

The typical areas of involvement are the extensor surfaces of the extremities, trunk, buttocks, and face. The palms and soles are not usually involved. Lesions are present at birth in up to one-third of patients.¹²³ Most begin to show evidence of involvement during the first year of life, with progression during childhood and stabilization at puberty. Later improvement has been described, including clearing with fevers.

Extracutaneous features

There are usually no extracutaneous features, although ataxia has been described.¹²⁴

Etiology and pathogenesis

Mutations in the *GJB3* gene which encodes for connexin 31,¹²⁵ and the *GJB4* gene which encodes for connexin 30.3,^{75,126} have been shown to cause erythrokeratoderma variabilis. There is likely to be further genetic heterogeneity as mutations in these two genes do not account for all cases of EKV.⁷⁵

Differential diagnosis

KID syndrome and Clouston syndrome can cause diagnostic confusion, but palmoplantar keratoderma is not usually a feature of EKV.

Treatment and care

Treatment with systemic retinoids has resulted in improvement or clearing.

CLOUSTON SYNDROME: HIDROTIC ECTODERMAL DYSPLASIA

Cutaneous features

This autosomal dominant genodermatosis was first described in a very extensive family of French Canadian extraction, who subsequently migrated to Scotland and the USA.^{76,127,128} The characteristic features are total alopecia, severe nail dystrophy, hyperpigmentation over the joints, strabismus, bulbous fingertips, and a distinctive palmoplantar keratoderma. In contrast to hypohidrotic ectodermal dysplasia, sweating is unimpaired and facial, dental, and breast development are normal.¹²⁹ The original kindred has been followed extensively for years, and

multiple cutaneous carcinomas of the nail bed and palmar tissue have been observed in several affected individuals.^{130–132}

Extracutaneous features

None.

Etiology and pathogenesis

In 1996, Clouston syndrome was linked to chromosome 13q11–q12.1,¹³³ and subsequent studies have shown genetic homogeneity to this locus.^{134–138} Recently, mutations in the *GJB6* gene encoding the β connexin 30 were identified in all available kindreds. Interestingly, only two mutations in *GJB6* (G11R and A88V) accounted for all the families tested.¹³⁹ Mutations in *GJB6* had previously been identified in a small family with dominant nonsyndromic hearing loss,¹⁴⁰ emphasizing the complexity and diversity of phenotypes caused by dominant-acting connexin mutations.

Differential diagnosis

Distinction from other connexin disorders such as KID syndrome and EKV is important and not always obvious. Alopecia is most commonly associated with Clouston syndrome. The stippled palmoplantar keratoderma is seen in both KID and Clouston syndromes.

Treatment and care

No specific treatment is needed in the neonatal period. In the older child the nail dystrophy can be severe and require podiatric attention. In some individuals the alopecia is a major issue: psychological support and wigs may be required.

ERYTHROKERATODERMA PROGRESSIVA SYMMETRICA (EPS)

Cutaneous features

This autosomal dominant disorder is characterized by symmetric erythematous scaling plaques that may spare the trunk but which are commonly found on the knees, buttocks, and groin. The palms and soles are affected in approximately 50% of patients, and the face is occasionally involved. Features are usually present during the first few years of life.

Extracutaneous features

There are usually no extracutaneous features.

Etiology and pathogenesis

Skin biopsies show acanthosis with perinuclear vacuolization of granular cells. Ultrastructural studies show lipid vacuoles in the stratum corneum, and increased numbers of swollen mitochondria in granular cells.¹⁴¹ Mutations in *loricrin* have been shown in some patients with this condition.^{142,143} Patients with these mutations may show features of Vohwinkel syndrome (VS), EPS, or CIE with a collodion baby phenotype at birth.¹⁴⁴ Common clinical features include hyperkeratosis of the palms and soles, with digital constriction. Histologic characteristics common to all of these conditions include parakeratotic hyperkeratosis with hypergranulosis, and nuclear accumulation of mutant *loricrin*. The term 'loricrin keratoderma' has been proposed to encompass all these phenotypes.¹⁴⁵ The molecular basis in individuals with no palmoplantar involvement is not clear.

Differential diagnosis

EKV can be distinguished from EPS by absence of palmoplantar involvement and transient migratory plaques (see Table 19.1).

Treatment and care

The use of oral retinoids has been reported to be effective. Topical keratolytics, retinoids, and glucocorticoids have also been used with more variable effects.¹⁴⁶

Palmoplantar keratodermas

Diffuse thickening of the skin on the palms and soles, known as palmoplantar keratoderma, is seen in a number of genetic disorders in infancy. In later life it is most commonly seen in pityriasis rubra pilaris and psoriasis.

The keratoderma of many forms of hereditary palmoplantar keratoderma (PPK) is first apparent during the first months of life, whereas in others (e.g., punctate keratoderma, keratoderma striata, Howell–Evans) it is not seen until early to late childhood.¹⁴⁷ In the neonatal period, the affected areas may appear hyperhydrated (Fig. 19.14). The majority of types of palmoplantar keratoderma are autosomal dominant. Some of the more common conditions are discussed briefly below.

In the Unna form of palmoplantar keratoderma (nonepidermolytic, i.e., not associated with fragile skin), the palms and soles are usually red at birth or soon thereafter. The skin progressively thickens on the palms and soles, starting at the



Figure 19.14 Palmoplantar keratoderma. (A,B) Note hyperhydrated skin with cracking and peeling.

margins and extending centrally, with red borders that usually disappear after several years. Keratotic lesions may occasionally be found on the dorsum of the hands and feet, the volar wrists, and the knees and elbows. The overall extent of involvement is variable. Palmoplantar hyperhidrosis is commonly associated with the nonepidermolytic form. A mild defect of keratin 1 and defects in keratins 6a and 16 have been described in families with nonepidermolytic palmoplantar keratoderma.¹⁴⁸ In Greither syndrome (transgrediens form, i.e., not confined to the volar aspect), the onset of thickening tends to be later, but the diffuse palmoplantar keratoderma extends onto the dorsum of the hands and feet. The knees, elbows, shins, and forearms are often involved. This syndrome is now known to be caused by mutations in keratin 1.^{149–151}

Vorner palmoplantar keratoderma (epidermolytic palmoplantar keratoderma) can also begin at an early age, and is clinically indistinguishable from the nonepidermolytic form during the first years of life, when the keratoderma is confined to the palms and soles. Epidermolytic palmoplantar keratoderma results from mutations in keratin 9, a gene that is only expressed in the skin of the palms and soles, limiting its distribution of expression. It should be noted that descendants of the family described by Thost¹⁵² as having nonepidermolytic palmoplantar keratoderma actually have keratin 9 mutations, demonstrating that the epidermolytic hyperkeratosis found in biopsy sections is an inconstant feature that may require several biopsies for detection.

The keratoses of Vohwinkel syndrome also are first noted shortly after birth, and gradually develop into the typical honeycombed diffuse palmoplantar hyperkeratoses with starfish-like keratoses on the backs of the hands, fingers, and toes. The constricting bands of the digits (pseudoinhum) first develop at 5 years of age or later, and can lead to autoamputation, as well as decreased motility of the hands. Some patients with Vohwinkel syndrome have alopecia, and an erythrokeratoderma has been described as well. The gene defect involves mutations in the gene that codes for loricrin.¹⁵³ Patients with deafness and the palmoplantar changes of Vohwinkel have connexin 26 mutations, not loricrin gene mutations.

Mal de Meleda, an autosomal recessive form of palmoplantar keratoderma, is not congenital but presents during the first 6 months of life as a diffuse palmoplantar keratoderma. The dorsal surfaces of the hands and feet are involved, and keratotic plaques tend to be present on the knees and elbows as well.¹⁵⁴ Koilonychia, nail thickening, and subungual hyperkeratosis are usually associated. Mild perioral erythema and hyperkeratosis may be present. Mal de Meleda is known to be caused by mutations in the secreted protein *SLURP1* gene.^{155,156}

OLMSTED SYNDROME

Cutaneous features

This extremely rare disorder usually presents with progressive thickening of the palms and soles during the first few years of life.¹⁵⁷ Typically, lesions are absent during the neonatal period, but begin as discrete lesions that become more confluent with time. The borders of keratoderma are erythematous. Contractures of the palms and soles, and autoamputation from progressive digital constriction are common. Lesions, particularly on the feet, tend to be exquisitely painful. After the onset of palmoplantar keratoderma the periorificial areas become

hyperkeratotic, with fissured plaques. This involvement of periorificial areas, particularly perioral, perianal, perinasal, pericrucial, and periumbilical, distinguishes this condition from other forms of palmoplantar keratoderma. Oral leukokeratosis, alopecia, and nail dystrophy have been described in association.

Extracutaneous features

There are no extracutaneous features.

Etiology and pathogenesis

Olmsted syndrome is caused by a missense mutation in *TRPV3*, expressed in skin, hair follicles, brain and spinal cord.¹⁵⁸

Differential diagnosis

Olmsted syndrome is usually easily distinguished from other mutilating keratodermas.

Treatment and care

In the neonatal period no specific care is necessary, and indeed keratolytics are best avoided as they do not tend to be helpful. In the older child, regular paring and sometimes grafting is needed to preserve good hand function and the ability to walk.

TYROSINEMIA II

Cutaneous features

Tyrosinemia II (Richner–Hanhart syndrome) is an autosomal recessive disorder comprising a triad of ocular manifestations, cutaneous hyperkeratoses, and mental retardation. The early cutaneous lesions may be seen during the first year of life as sharply demarcated, yellowish keratotic papules of the palmar and plantar surfaces, but more commonly appear later, sometimes as late as the second decade. The lesions become more erythematous, erosive, and painful with time. In one case the clinical phenotype was of a diffuse PPK.¹⁵⁹ Nail dystrophy may also be associated.

Extracutaneous features

The ocular manifestations of the disorder appear soon after birth.¹⁶⁰ Photophobia and bilateral tearing commonly occur within the first 3 months of life, and progress to corneal erosions. Ocular lesions are typically transitory, and are subject to intermittent relapses. The corneal lesions are frequently misdiagnosed as herpetic keratitis, and remissions may be misinterpreted as a response to antiviral therapy. The eye changes occasionally develop after the skin manifestations. Varying degrees of intellectual impairment have been described in less than half of affected patients.

Etiology and pathogenesis

Tyrosinemia type II is caused by a deficiency of hepatic tyrosine aminotransferase (TAT)¹⁶¹ that results in elevated tyrosine levels in the plasma and urine.

Differential diagnosis

Diagnosis is occasionally delayed until adulthood. Early diagnosis is important, as appropriate dietary advice can help diminish the severity of neurological and ocular manifestations. In the neonate the corneal erosions can be mistaken for herpetic infections. The focal PPK that occurs later in life can resemble that associated with keratin 6A, 6B, 16, and 17 mutations, but may be more erosive.

Treatment and care

The treatment of choice is dietary restriction of tyrosine with a low-phenylalanine, low-tyrosine diet.

KERATOSIS LINEARIS WITH ICHTHYOSIS CONGENITA AND SCLEROSING KERATODERMA: KCLICK SYNDROME

Cutaneous features

KCLICK syndrome is an autosomal recessive disorder characterized by palmoplantar transgressive keratoderma, congenital ichthyosis and linear hyperkeratotic plaques in the flexor regions.¹⁶²

Extracutaneous features

None.

Etiology and pathogenesis

KCLICK syndrome is caused by a single-nucleotide deletion in the proteasome maturation protein (*POMP*) gene leading to aberrant processing of profilaggrin to filaggrin.¹⁶³ Histopathology reveals an epidermis with acanthosis, hypergranulosis and hyperkeratosis and at electron microscopy numerous keratohyalin granules are found in the keratinocytes of the granular layer.¹⁶²

Differential diagnosis

Differential diagnoses include KID syndrome, Vohwinkel syndrome, Olmsted syndrome and the generalized forms of congenital ichthyosis.¹⁶²

Treatment and care

Treatment with topical keratolytics and oral retinoids results in significant improvement but recurrence is common once treatment is stopped.¹⁶²

Restrictive dermopathy

Cutaneous features

Neonates with this lethal autosomal recessive condition are born with rigid skin, attributed to fetal akinesia or hypokinesia deformation sequence.^{164–166} Polyhydramnios with reduced fetal movements usually results in premature delivery at

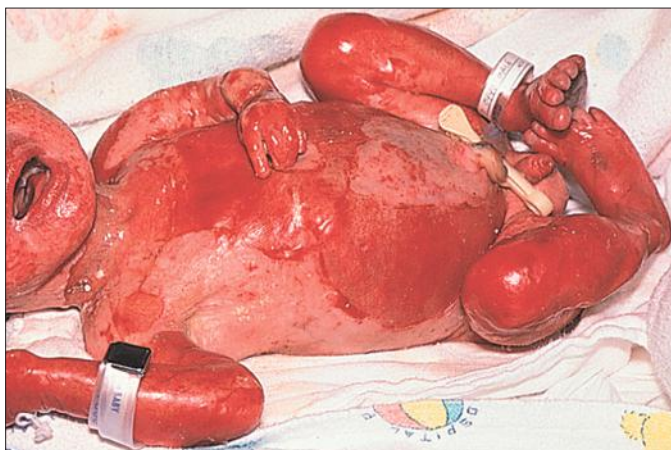


Figure 19.15 Eroded, shiny skin is seen in this neonate with restrictive dermopathy.

approximately 31 weeks' gestational age. Premature rupture of the membranes and an enlarged placenta with a short umbilical cord are often associated. The skin typically is thin, shiny, and red, with prominent vessels. Scaling and erosions are frequently seen (Fig. 19.15).

Extracutaneous features

The facies are characterized by micrognathia, a small open mouth (O-shaped), pinched nares with choanal atresia or stenosis, and flattened or low-set pinnae. The constraint of movement in utero also leads to flexion contractures of the joints, and bony changes such as poor ossification of the clavicle; over-tubulation of the radius, ulna, and distal phalanges; and widened sutures and large fontanelles. Natal teeth have been described in 25–50% of patients with restrictive dermopathy. Most patients die of pulmonary hypoplasia with respiratory insufficiency or sepsis.

Etiology and pathogenesis

Restrictive dermopathy may be caused by dominant de novo *LMNA* (encoding lamin A) mutations¹⁶⁷ or, more frequently, by recessive null *ZMPSTE24* mutations, most of which lie in a mutational hotspot within exon 9.¹⁶⁸ This gene encodes a metalloproteinase specifically involved in the post-translational processing of lamin A. It is likely that many of the dysmorphic features observed in restrictive dermopathy are secondary to restricted fetal movement; this condition has been termed fetal akinesia deformation sequence (FADS).⁹³

Differential diagnosis

Skin biopsy at 20 weeks' gestational age may be normal,¹⁶⁹ and DNA-based prenatal diagnosis is best if the familial gene defect is known. The onset of intrauterine growth retardation, restricted fetal movement, and polyhydramnios that raise suspicion of the diagnosis may occur late in gestation, precluding prenatal testing. Histopathologic examination of skin biopsy sections shows a thick epidermis, and a thin dermis with a paucity and hypoplasia of cutaneous appendages. Collagen bundles are abnormally arranged, and elastic fibers are almost absent.

Treatment and care

Most patients die during the neonatal period; the longest survivor with restrictive dermopathy died at 4 months of age.

Neu-laxova syndrome

Cutaneous features

Neu-Laxova syndrome is a rare, lethal, autosomal recessive trait characterized by severe intrauterine growth retardation, microcephaly with abnormal brain development, edema, and ichthyosis.^{170,171} The ichthyosis is present at birth, but varies from mildly scaling skin to a harlequin fetus appearance. Histologic findings are nonspecific and show the acanthosis and orthokeratosis of lamellar ichthyosis. Excessive subcutaneous adipose tissue and myxomatous connective tissue may contribute to the characteristic edema.

Extracutaneous features

The lack of brain development is characterized by lissencephaly and agenesis of the corpus callosum. Characteristic facial

features include a slanted forehead, protuberant eyes, a flattened nose, deformed ears, micrognathia, and a short neck. Microphthalmia and cleft palate are occasionally associated. The limbs, fingers, and toes are abnormal, with syndactyly, hypoplasia, and contractures. Skeletal X-rays often show poor mineralization. The craniofacial and limb abnormalities are related to the reduced intrauterine movement, and are therefore defined as fetal akinesia/hypokinesia sequence, as has been described in other syndromes.

Etiology and pathogenesis

The etiology of this rare and devastating disorder is unknown, but the term is likely to cover a number of heterogeneous disorders.¹⁷²

Differential diagnosis

The constellation of features usually makes the diagnosis clear.

Treatment and care

Treatment is palliative.

Neonatal scaling of hypohidrotic ectodermal dysplasia

The ectodermal dysplasias encompass a complex and highly diverse group of heritable disorders that share in common

developmental abnormalities of ectodermal appendages (see [Chapter 25](#)). The most common form is hypohidrotic ectodermal dysplasia, which is most commonly X-linked, but can be autosomal dominant or autosomal recessive. Scaling of the skin during the newborn period has been described in 70% of patients with X-linked hypohidrotic ectodermal dysplasia.¹⁷³ The skin has been described as 'like plastic,' peeling off in sheets, and 'like a snake peeling.' Some infants have been described as being very dry at birth, and others as having a collodion membrane-like scale. Later in infancy the typical facial features, sparsity of hair, decreased ability to sweat, and eventually dental abnormalities allow the diagnosis to be confirmed. Patients tend to have an increased risk of upper respiratory tract infections and atopy, particularly manifesting as asthma and atopic dermatitis. The genetic defects underlying both X-linked and autosomal forms of hypohidrotic ectodermal dysplasia encode proteins of the ectodysplasin/NFκB signaling pathways.¹⁷⁴

Access the full reference list at ExpertConsult.com 

KEY REFERENCES

- Oji V, Tadini G, Akiyama M, et al. Revised nomenclature and classification of inherited ichthyoses: results of the first Ichthyosis Consensus Conference in Sorèze 2009. *J Am Acad Dermatol* 2010;63:607–41.
- Vahlquist A, Bygum A, Gånemo A, et al. Genotypic and clinical spectrum of self-improving collodion ichthyosis: ALOX12B, ALOXE3, and TGM1 mutations in Scandinavian patients. *J Invest Dermatol* 2010;130:438–43.
- Paller AS, van Steensel MA, Rodriguez-Martín M, et al. Pathogenesis-based therapy reverses cutaneous abnormalities in an inherited disorder of distal cholesterol metabolism. *J Invest Dermatol* 2011;131:2242–8.
- Bitoun E, Chavanas S, Irvine AD, et al. Netherton syndrome: disease expression and spectrum of SPINK5 mutations in 21 families. *J Invest Dermatol* 2002;118:352–61.
- Bergmann E, Egly JM. Trichothiodystrophy, a transcription syndrome. *Trends Genet* 2001;17:279–86.
- De Laurenzi V, Rogers GR, Hamrock DJ, et al. Sjögren–Larsson syndrome is caused by mutations in the fatty aldehyde dehydrogenase gene. *Nat Genet* 1996;12:52–7.
- Jan AY, Amin S, Ratajczak P, et al. Genetic heterogeneity of KID syndrome: identification of a Cx30 gene (GJB6) mutation in a patient with KID syndrome and congenital atrichia. *J Invest Dermatol* 2004;122:1108–13.
- Rajpopat S, Moss C, Mellerio J, et al. Harlequin ichthyosis: A review of clinical and molecular findings in 45 cases. *Arch Dermatol* 2011;147:681–6.
- Kelsell DP, Norgett EE, Unsworth H, et al. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. *Am J Hum Genet* 2005;76:794–803.
- Israeli S, Khamaysi Z, Fuchs-Telem D, et al. A mutation in LIPN, encoding epidermal lipase N, causes a late-onset form of autosomal-recessive congenital ichthyosis. *Am J Hum Genet* 2011;88:482–7.

REFERENCES

- Oji V, Tadini G, Akiyama M, et al. Revised nomenclature and classification of inherited ichthyoses: results of the first Ichthyosis Consensus Conference in Sorèze 2009. *J Am Acad Dermatol* 2010;63:607–41.
- Larregue M, Gharbi R, Daniel J, et al. Colloidion baby. Clinical course based on 29 cases. *Ann Dermatol Syphiligr (Paris)* 1976;103:31–56.
- Lui K, Commens C, Choong R, et al. Colloidion babies with Gaucher's disease. *Arch Dis Child* 1988;63:854–6.
- Frenk E, de Techtermann F. Self-healing colloidion baby: evidence for autosomal recessive inheritance. *Pediatr Dermatol* 1992;9:95–7.
- Buyse L, Graves C, Marks R, et al. Colloidion baby dehydration: the danger of high transepidermal water loss. *Br J Dermatol* 1993;129:86–8.
- Garty BZ, Wiseman Y, Metzker A, et al. Hypernatremic dehydration and hypothermia in congenital lamellar ichthyosis. *Pediatr Dermatol* 1985;3:65–8.
- Perlman M, Bar-Ziv J. Congenital ichthyosis and neonatal pulmonary disease. *Pediatrics* 1974;53:573–5.
- Raghunath M, Hennies H-C, Ahvazi B, et al. Self-healing colloidion baby: a dynamic phenotype explained by a particular transglutaminase-1 mutation. *J Invest Dermatol* 2003;120:224–8.
- Vahlquist A, Bygum A, Gånemo A, et al. Genotypic and clinical spectrum of self-improving colloidion ichthyosis: ALOX12B, ALOXE3, and TGM1 mutations in Scandinavian patients. *J Invest Dermatol* 2010;130:438–43.
- Wells RS, Kerr CB. Clinical features of autosomal dominant and sex-linked ichthyosis in an English Population. *BMJ* 1966;1:947–50.
- Lefèvre C, Audebert S, Jobard F, et al. Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2. *Hum Mol Genet* 2003;12:2369–78.
- Dale BA, Holbrook KA, Fleckman P, et al. Heterogeneity in harlequin ichthyosis, an inborn error of epidermal keratinization: variable morphology and structural protein expression and a defect in lamellar granules. *J Invest Dermatol* 1990;94:6–18.
- Hamm H, Meinecke P, Traupe H. Further delineation of the ichthyosis follicularis, atrichia, and photophobia syndrome. *Eur J Pediatr* 1991;150:627–9.
- Eramo LR, Esterly NB, Zieserl EJ, et al. Ichthyosis follicularis with alopecia and photophobia. *Arch Dermatol* 1985;121:1167–74.
- Zeligman I, Fleisher TL. Ichthyosis follicularis. *Arch Dermatol* 1959;80:413–20.
- Happle R. What is IFAP syndrome? *Am J Med Genet A* 2004;124A:328.
- Mégarbané H, Zablit C, Waked N, et al. Ichthyosis follicularis, alopecia, and photophobia (IFAP) syndrome: report of a new family with additional features and review. *Am J Med Genet A* 2004;124A:323–7.
- Traboulsi E, Waked N, Mégarbané H, et al. Ocular findings in ichthyosis follicularis–alopecia–photophobia (IFAP) syndrome. *Ophthalmic Genet* 2004;25:153–6.
- Tsolia M, Aroni K, Konstantopoulou I, et al. Ichthyosis follicularis with alopecia and photophobia in a girl with cataract: histological and electron microscopy findings. *Acta Derm Venereol* 2005;85:51–5.
- Oeffner F, Fischer G, Happle R, et al. IFAP syndrome is caused by deficiency in MBTPS2, an intramembrane zinc metalloprotease essential for cholesterol homeostasis and ER stress response. *Am J Hum Genet* 2009;84:459–67.
- König A, Happle R. Linear lesions reflecting lyonization in women heterozygous for IFAP syndrome (ichthyosis follicularis with atrichia and photophobia). *Am J Med Genet* 1999;85:365–8.
- Khandpur S, Bhat R, Ramam M. Ichthyosis follicularis, alopecia and photophobia (IFAP) syndrome treated with acitretin. *J Eur Acad Dermatol Venereol* 2005;19:759–62.
- Happle R. X-linked dominant chondrodysplasia punctata/ichthyosis/follicularis syndrome in males. *Am J Med Genet* 1995;57:493.
- Kalter DC, Atherton DJ, Clayton PT. X-linked dominant Conradi–Hünemann syndrome presenting as congenital erythroderma. *J Am Acad Dermatol* 1989;21:248–56.
- Cañueto J, Gíros M, Ciria S, et al. Clinical, molecular and biochemical characterization of nine Spanish families with Conradi–Hünemann–Happle Syndrome: new insights into X-linked dominant chondrodysplasia punctata with a comprehensive review of the literature. *Br J Dermatol* 2012;166(4):830–8.
- Has C, Bruckner-Tuderman L, Müller D, et al. The Conradi–Hünemann–Happle syndrome (CDPX2) and emopamil binding protein: novel mutations, and somatic and gonadal mosaicism. *Hum Mol Genet* 2000;9:1951–5.
- Bick D, Curry CJ, McGill JR, et al. Male infant with ichthyosis, Kallmann syndrome, chondrodysplasia punctata, and an Xp chromosome deletion. *Am J Med Genet* 1989;33:100–7.
- Happle R, Effendy I, Megahed M, et al. CHILD syndrome in a boy. *Am J Med Genet* 1996;62:192–4.
- Hebert AA, Esterly NB, Holbrook KA, et al. The CHILD syndrome. Histologic and ultrastructural studies. *Arch Dermatol* 1987;123:503–9.
- Happle R. Psychotropism as a cutaneous feature of the CHILD syndrome. *J Am Acad Dermatol* 1990;23:763–6.
- Baptista AP, Cortesao JM. [Inflammatory variable epidermal naevus (atypical I.L.V.E.N.? A new entity?) (author's transl)]. *Ann Dermatol Venereol* 1979;106:443–50.
- König A, Happle R, Bornholdt D, et al. Mutations in the NSDHL gene, encoding a 3beta-hydroxysteroid dehydrogenase, cause CHILD syndrome. *Am J Med Genet* 2000;90:339–46.
- Paller AS, van Steensel MA, Rodriguez-Martin M, et al. Pathogenesis-based therapy reverses cutaneous abnormalities in an inherited disorder of distal cholesterol metabolism. *J Invest Dermatol* 2011;131:2242–8.
- Judge MR, Morgan G, Harper JJ. A clinical and immunological study of Netherton's syndrome. *Br J Dermatol* 1994;131:615–21.
- Chavanas S, Bodemer C, Rochat A, et al. Mutations in SPINK5, encoding a serine protease inhibitor, cause Netherton syndrome. *Nat Genet* 2000;25:141–2.
- Bitoun E, Chavanas S, Irvine AD, et al. Netherton syndrome: disease expression and spectrum of SPINK5 mutations in 21 families. *J Invest Dermatol* 2002;118:352–61.
- Ishida-Yamamoto A, Deraison C, Bonnart C, et al. LEKTI is localized in lamellar granules, separated from KLK5 and KLK7, and is secreted in the extracellular spaces of the superficial stratum granulosum. *J Invest Dermatol* 2005;124:360–6.
- Descargues P, Deraison C, Bonnart C, et al. Spink5-deficient mice mimic Netherton syndrome through degradation of desmoglein 1 by epidermal protease hyperactivity. *Nat Genet* 2005;37:56–65.
- Scheimberg I, Hoeger PH, Harper JJ, et al. Omenn's syndrome: differential diagnosis in infants with erythroderma and immunodeficiency. *Pediatr Dev Pathol* 2001;4:237–45.
- Ong C, O'Toole EA, Ghali L, et al. LEKTI demonstrable by immunohistochemistry of the skin: a potential diagnostic skin test for Netherton syndrome. *Br J Dermatol* 2004;151:1253–7.
- Allen A, Siegfried E, Silverman R, et al. Significant absorption of topical tacrolimus in 3 patients with Netherton syndrome. *Arch Dermatol* 2001;137:747–50.
- Nagtzaam IF, van Geel M, Driessen A, et al. Bile duct paucity is part of the neonatal ichthyosis-sclerosing cholangitis phenotype. *Br J Dermatol* 2010;163:205–7.
- Hadj-Rabia S, Baala L, Vabres P, et al. Claudin-1 gene mutations in neonatal sclerosing cholangitis associated with ichthyosis: a tight junction disease. *Gastroenterology* 2004;127:1386–90.
- Feldmeyer L, Huber M, Fellmann F, et al. Confirmation of the origin of NISCH syndrome. *Hum Mutat* 2006;27:408–10.
- Brusasco A, Restano L. The typical 'tiger tail' pattern of the hair shaft in trichothiodystrophy may not be evident at birth. *Arch Dermatol* 1997;133:249.
- Hersh JH, Klein LR, Joyce MR, et al. Trichothiodystrophy and associated anomalies: a variant of SIBIDS or new symptom complex? *Pediatr Dermatol* 1993;10:117–22.
- Bergmann E, Egly JM. Trichothiodystrophy, a transcription syndrome. *Trends Genet* 2001;17:279–86.
- Cleaver JE. Splitting hairs – discovery of a new DNA repair and transcription factor for the human disease trichothiodystrophy. *DNA Repair (Amst)* 2005;4:285–7.
- Vermeulen W, Bergmann E, Auriol J, et al. Sublimiting concentration of TFIIF transcription/DNA repair factor causes TTD-A trichothiodystrophy disorder. *Nat Genet* 2000;26:307–13.
- Giglia-Mari G, Coin F, Ranish JA, et al. A new, tenth subunit of TFIIF is responsible for the DNA repair syndrome trichothiodystrophy group A. *Nat Genet* 2004;36:714–19.
- Sarasin A, Blanchet-Bardon C, Renault G, et al. Prenatal diagnosis in a subset of trichothiodystrophy patients defective in DNA repair. *Br J Dermatol* 1992;127:485–91.
- Jagell S, Lidén S. Ichthyosis in the Sjögren–Larsson syndrome. *Clin Genet* 1982;21:243–52.
- Lacour M. Update on Sjögren–Larsson syndrome. *Dermatology* 1996;193:77–82.
- Rizzo WB. Sjögren–Larsson syndrome. *Semin Dermatol* 1993;12:210–18.
- Ito M, Oguro K, Sato Y. Ultrastructural study of the skin in Sjögren–Larsson syndrome. *Arch Dermatol Res* 1991;283:141–8.
- Willemssen MAA, Ijlst L, Steijlen PM, et al. Clinical, biochemical and molecular genetic

- characteristics of 19 patients with the Sjögren-Larsson syndrome. *Brain* 2001;124:1426–37.
57. Nigro JF, Rizzo WB, Esterly NB. Redefining the Sjögren-Larsson syndrome: atypical findings in three siblings and implications regarding diagnosis. *J Am Acad Dermatol* 1996;35:678–84.
 58. De Laurenzi V, Rogers GR, Hamrock DJ, et al. Sjögren-Larsson syndrome is caused by mutations in the fatty aldehyde dehydrogenase gene. *Nat Genet* 1996;12:52–7.
 59. Sillén A, Jagell S, Wadelius C. A missense mutation in the FALDH gene identified in Sjögren-Larsson syndrome patients originating from the northern part of Sweden. *Hum Genet* 1997;100:201–3.
 60. Willemsen MA, Rotteveel JJ, Steijlen PM, et al. 5-Lipoxygenase inhibition: a new treatment strategy for Sjögren-Larsson syndrome. *Neuropediatrics* 2000;31:1–3.
 61. Fujimoto A, Tayebi N, Sidransky E. Congenital ichthyosis preceding neurologic symptoms in two sibs with type 2 Gaucher disease. *Am J Med Genet* 1995;59:356–8.
 62. Sidransky E, Sherer DM, Ginns EI. Gaucher disease in the neonate: a distinct Gaucher phenotype is analogous to a mouse model created by targeted disruption of the glucocerebrosidase gene. *Pediatr Res* 1992;32:494–8.
 63. Goker-Alpan O, Schiffmann R, Park JK, et al. Phenotypic continuum in neuronopathic Gaucher disease: an intermediate phenotype between type 2 and type 3. *J Pediatr* 2003;143:273–6.
 64. Charrow J, Andersson HC, Kaplan P, et al. The Gaucher Registry: Demographics and disease characteristics of 1698 patients with Gaucher disease. *Arch Intern Med* 2000;160:2835–43.
 65. Grabowski GA. Recent clinical progress in Gaucher disease. *Curr Opin Pediatr* 2005;17:519–24.
 66. Deegan PB, Moran MT, McFarlane I, et al. Clinical evaluation of chemokine and enzymatic biomarkers of Gaucher disease. *Blood Cells Mol Dis* 2005;35:259–67.
 67. Caceres-Rios H, Tamayo-Sanchez L, Duran-Mckinster C, et al. Keratitis, ichthyosis, and deafness (KID syndrome): review of the literature and proposal of a new terminology. *Pediatr Dermatol* 1996;13:105–13.
 68. Sonoda S, Uchino E, Sonoda KH, et al. Two patients with severe corneal disease in KID syndrome. *Am J Ophthalmol* 2004;137:181–3.
 69. Harms M, Gilardi S, Levy PM, et al. KID syndrome (keratitis, ichthyosis, and deafness) and chronic mucocutaneous candidiasis: case report and review of the literature. *Pediatr Dermatol* 1984;2:1–7.
 70. Janecke AR, Hennies HC, Günther B, et al. GJB2 mutations in keratitis-ichthyosis-deafness syndrome including its fatal form. *Am J Med Genet A* 2005;133A:128–31.
 71. Richard G, Rouan F, Willoughby CE, et al. Missense mutations in GJB2 encoding connexin-26 cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome. *Am J Hum Genet* 2002;70:1341–8.
 72. Jan AY, Amin S, Ratajczak P, et al. Genetic heterogeneity of KID syndrome: identification of a Cx30 gene (GJB6) mutation in a patient with KID syndrome and congenital atrichia. *J Invest Dermatol* 2004;122:1108–13.
 73. Pitts JD. The discovery of metabolic co-operation. *Bioessays* 1998;20:1047–51.
 74. Choudhry R, Pitts JD, Hodgins MB. Changing patterns of gap junctional intercellular communication and connexin distribution in mouse epidermis and hair follicles during embryonic development. *Dev Dyn* 1997;210:417–30.
 75. Common JE, O'Toole EA, Leigh IM, et al. Clinical and genetic heterogeneity of erythrodermatoderma variabilis. *J Invest Dermatol* 2005;125:920–7.
 76. Clouston HR. A hereditary ectodermal dystrophy. *Can Med Assoc J* 1929;21:18–31.
 77. Hampton SM, Toner JG, Small J. Cochlear implant extrusion in a child with keratitis, ichthyosis and deafness syndrome. *J Laryngol Otol* 1997;111:465–7.
 78. Shiraishi S, Murakami S, Miki Y. Oral fluconazole treatment of fungating candidiasis in the keratitis, ichthyosis and deafness (KID) syndrome. *Br J Dermatol* 1994;131:904–7.
 79. Igal RA, Rhoads JM, Coleman RA. Neutral lipid storage disease with fatty liver and cholestasis. *J Pediatr Gastroenterol Nutr* 1997;25:541–7.
 80. Chanarin I, Patel A, Slavin G, et al. Neutral-lipid storage disease: a new disorder of lipid metabolism. *BMJ* 1975;1:553–5.
 81. Dorfman ML, Hershko C, Eisenberg S, et al. Ichthyosiform dermatosis with systemic lipodosis. *Arch Dermatol* 1974;110:261–6.
 82. Lefevre C, Jobard F, Caux F, et al. Mutations in CGI-58, the gene encoding a new protein of the esterase/lipase/thioesterase subfamily, in Chanarin-Dorfman syndrome. *Am J Hum Genet* 2001;69:1002–12.
 83. Jordans GH. The familial occurrence of fat containing vacuoles in the leukocytes diagnosed in two brothers suffering from dystrophia musculorum progressiva (ERB). *Acta Med Scand* 1953;145:419–23.
 84. Kakourou T, Drogari E, Christomanou H, et al. Neutral lipid storage disease – response to dietary intervention. *Arch Dis Child* 1997;77:184.
 85. Klar J, Gedde-Dahl T Jr, Larsson M, et al. Assignment of the locus for ichthyosis prematurity syndrome to chromosome 9q33.3–34.13. *J Med Genet* 2004;41:208–12.
 86. Khnykin D, Rønnevig J, Johnsson M, et al. Ichthyosis prematurity syndrome: clinical evaluation of 17 families with a rare disorder of lipid metabolism. *J Am Acad Dermatol* 2012;66:606–16.
 87. Klar J, Schweiger M, Zimmerman R, et al. Mutations in the fatty acid transport protein 4 gene cause the ichthyosis prematurity syndrome. *Am J Hum Genet* 2009;85:248–53.
 88. Sidbury R, Paller AS. What syndrome is this? CHIME syndrome. *Pediatr Dermatol* 2001;18:252–4.
 89. Tinschert S, Anton-Lamprecht I, Albrecht-Nebe H, et al. Zurich neuroectodermal syndrome: migratory ichthyosiform dermatosis, colobomas, and other abnormalities. *Pediatr Dermatol* 1996;13:363–71.
 90. Shashi V, Zunich J, Kelly TE, et al. Neuroectodermal (CHIME) syndrome: an additional case with long term follow up of all reported cases. *J Med Genet* 1995;32:465–9.
 91. Ng BG, Hackmann K, Jones MA, et al. Mutations in the glycosylphosphatidylinositol gene PIGL cause CHIME syndrome. *Am J Hum Genet* 2012;90:685–8.
 92. Montpetit A, Côté S, Brusteine E, et al. Disruption of AP1S1, causing a novel neurocutaneous syndrome, perturbs development of the skin and spinal cord. *PLoS Genet* 2008;4:e1000296.
 93. Witters I, Moerman P, Fryns JP. Fetal akinesia deformation sequence: a study of 30 consecutive in utero diagnoses. *Am J Med Genet* 2002;113:23–8.
 94. Haftek M, Cambazard F, Dhoubailly D, et al. A longitudinal study of a harlequin infant presenting clinically as non-bullous congenital ichthyosiform erythroderma. *Br J Dermatol* 1996;135:448–53.
 95. Prasad RS, Pejaver RK, Hassan A, et al. Management and follow-up of harlequin siblings. *Br J Dermatol* 1994;130:650–3.
 96. Roberts LJ. Long-term survival of a harlequin fetus. *J Am Acad Dermatol* 1989;21:335–9.
 97. Rogers M, Scraf C. Harlequin baby treated with etretinate. *Pediatr Dermatol* 1989;6:216–21.
 98. Ward PS, Jones RD. Successful treatment of a harlequin fetus. *Arch Dis Child* 1989;64:1309–11.
 99. Lawlor F, Peiris S. Harlequin fetus successfully treated with etretinate. *Br J Dermatol* 1985;112:585–90.
 100. Rajpopat S, Moss C, Mellerio J, et al. Harlequin ichthyosis: A review of clinical and molecular findings in 45 cases. *Arch Dermatol* 2011;147:681–6.
 101. Akiyama M, Sugiyama-Nakagiri Y, Sakai K, et al. Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer. *J Clin Invest* 2005;115:1777–84.
 102. Traupe H, Kolde G, Happle R. Autosomal dominant lamellar ichthyosis: a new skin disorder. *Clin Genet* 1984;26:457–61.
 103. Williams ML, Elias PM. Heterogeneity in autosomal recessive ichthyosis. Clinical and biochemical differentiation of lamellar ichthyosis and nonbullous congenital ichthyosiform erythroderma. *Arch Dermatol* 1985;121:477–88.
 104. Oji V, Hautier JM, Ahvazi B, et al. Bathing suit ichthyosis is caused by transglutaminase-1 deficiency: evidence for a temperature-sensitive phenotype. *Hum Mol Genet* 2006;15:3083–97.
 105. Fischer J. Autosomal recessive congenital ichthyosis. *J Invest Dermatol* 2009;129:1319–21.
 106. Grall A, Guaguère E, Planchais S, et al. PNPLA1 mutations cause autosomal recessive congenital ichthyosis in golden retriever dogs and humans. *Nat Genet* 2012;44:140–7.
 107. Huber M, Rettler I, Bernasconi K, et al. Mutations of keratinocyte transglutaminase in lamellar ichthyosis. *Science* 1995;267:525–8.
 108. De Juanes S, Epp N, Latzko S, et al. Development of an ichthyosiform phenotype in Alox12b-deficient mouse skin transplants. *J Invest Dermatol* 2009;129:1429–36.
 109. Kelsell DP, Norgett EE, Unsworth H, et al. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. *Am J Hum Genet* 2005;76:794–803.
 110. Hovnanian A. Harlequin ichthyosis unmasked: a defect of lipid transport. *J Clin Invest* 2005;115:1708–10.
 111. Israeli S, Khamaysi Z, Fuchs-Telem D, et al. A mutation in LIPN, encoding epidermal lipase N, causes a late-onset form of autosomal-recessive congenital ichthyosis. *Am J Hum Genet* 2011;88:482–7.
 112. Schorderet DF, Huber M, Laurini RN, et al. Prenatal diagnosis of lamellar ichthyosis by

- direct mutational analysis of the keratinocyte transglutaminase gene. *Prenat Diagn* 1997;17:483–6.
113. Sahn EE, Weimer CE Jr, Garen PD. Annular epidermolytic ichthyosis: a unique phenotype. *J Am Acad Dermatol* 1992;27:348–55.
 114. Paller AS. Lessons from skin blistering: molecular mechanisms and unusual patterns of inheritance? *Am J Pathol* 1996;148:1727–31.
 115. Irvine AD, McLean WH. Human keratin diseases: the increasing spectrum of disease and subtlety of the phenotype–genotype correlation. *Br J Dermatol* 1999;140:815–28.
 116. Golbus MS, Sagebiel RW, Filly RA, et al. Prenatal diagnosis of congenital bullous ichthyosiform erythroderma (epidermolytic hyperkeratosis) by fetal skin biopsy. *N Engl J Med* 1980;302:93–5.
 117. Rothnagel JA, Longley MA, Holder RA, et al. Prenatal diagnosis of epidermolytic hyperkeratosis by direct gene sequencing. *J Invest Dermatol* 1994;102:13–16.
 118. Kanerva L, Karvonen J, Oikarinen A, et al. Ichthyosis hystrix (Curth–Macklin). Light and electron microscopic studies performed before and after etretinate treatment. *Arch Dermatol* 1984;120:1218–23.
 119. Sprecher E, Ishida-Yamamoto A, Becker OM, et al. Evidence for novel functions of the keratin tail emerging from a mutation causing ichthyosis hystrix. *J Invest Dermatol* 2001;116:511–19.
 120. Richardson ES, Lee JB, Hyde PH, et al. A novel mutation and large size polymorphism affecting the V2 domain of keratin 1 in an African-American family with severe, diffuse palmoplantar keratoderma of the ichthyosis hystrix Curth–Macklin type. *J Invest Dermatol* 2006;126:79–84.
 121. Bonifas JM, Bare JW, Chen MA, et al. Evidence against keratin gene mutations in a family with ichthyosis hystrix Curth–Macklin. *J Invest Dermatol* 1993;101:890–1.
 122. Oji V, Eckl KM, Aufenvenne K, et al. Loss of corneodesmin leads to severe skin barrier defect, pruritis, and atopy: unraveling the peeling skin disease. *Am J Hum Gen* 2010;87:274–81.
 123. Knipe RC, Flowers FP, Johnson FR Jr, et al. Erythrokeratoderma variabilis: case report and review of the literature. *Pediatr Dermatol* 1995;12:21–3.
 124. Giroux JM, Barbeau A. Erythrokeratoderma with ataxia. *Arch Dermatol* 1972;106:183–8.
 125. Richard G, Smith LE, Bailey RA, et al. Mutations in the human connexin gene GJB3 cause erythrokeratoderma variabilis. *Nat Genet* 1998;20:366–9.
 126. Macari F, Landau M, Cousin P, et al. Mutation in the gene for connexin 30.3 in a family with erythrokeratoderma variabilis. *Am J Hum Genet* 2000;67:1296–301.
 127. MacKay H, Davidson AM. Congenital ectodermal defect. *Br J Dermatol* 1929;41:1–5.
 128. Joachim H. Hereditary dystrophy of the hair and nails in six generations. *Ann Intern Med* 1936;10:400–2.
 129. Hassed SJ, Kincannon JM, Arnold GL. Clouston syndrome: an ectodermal dysplasia without significant dental findings. *Am J Med Genet* 1996;61:274–6.
 130. Campbell CJ, Keokarn T. Squamous-cell carcinoma of the nail bed in epidermal dysplasia. *J Bone Joint Surg Am* 1966;48:92–9.
 131. Mauro JA, Maslyn R, Stein AA. Squamous-cell carcinoma of nail bed in hereditary ectodermal dysplasia. *N Y State J Med* 1972;72:1065–6.
 132. Williams M, Fraser FC. Hydrotic ectodermal dysplasia – Clouston's family revisited. *Can Med Assoc J* 1967;96:36–8.
 133. Kibar Z, Der Kaloustian VM, Brais B, et al. The gene responsible for Clouston hidrotic ectodermal dysplasia maps to the pericentromeric region of chromosome 13q. *Hum Mol Genet* 1996;5:543–7.
 134. Kibar Z, Dubé MP, Powell J, et al. Clouston hidrotic ectodermal dysplasia (HED): genetic homogeneity, presence of a founder effect in the French Canadian population and fine genetic mapping. *Eur J Hum Genet* 2000;8:372–80.
 135. Lamartine J, Laoudj D, Blanchet-Bardon C, et al. Refined localization of the gene for Clouston syndrome (hidrotic ectodermal dysplasia) in a large French family. *Br J Dermatol* 2000;142:248–52.
 136. Radhakrishna U, Blouin JL, Mehenni H, et al. The gene for autosomal dominant hidrotic ectodermal dysplasia (Clouston syndrome) in a large Indian family maps to the 13q11–q12.1 pericentromeric region. *Am J Med Genet* 1997;71:80–6.
 137. Stevens HP, Choon SE, Hennies HC, et al. Evidence for a single genetic locus in Clouston's hidrotic ectodermal dysplasia. *Br J Dermatol* 1999;140:963–4.
 138. Taylor TD, Hayflick SJ, McKinnon W, et al. Confirmation of linkage of Clouston syndrome (hidrotic ectodermal dysplasia) to 13q11–q12.1 with evidence for multiple independent mutations. *J Invest Dermatol* 1998;111:83–5.
 139. Lamartine J, Munhoz Essenfelder G, Kibar Z, et al. Mutations in GJB6 cause hidrotic ectodermal dysplasia. *Nat Genet* 2000;26:142–4.
 140. Grifa A, Wagner CA, D'Ambrosio L, et al. Mutations in GJB6 cause nonsyndromic autosomal dominant deafness at DFNA3 locus. *Nat Genet* 1999;23:16–18.
 141. Nazzaro V, Blanchet-Bardon C. Progressive symmetric erythrokeratoderma. Histological and ultrastructural study of patient before and after treatment with etretinate. *Arch Dermatol* 1986;122:434–40.
 142. Ishida-Yamamoto A, McGrath JA, Lam H, et al. The molecular pathology of progressive symmetric erythrokeratoderma: a frameshift mutation in the loricrin gene and perturbations in the cornified cell envelope. *Am J Hum Genet* 1997;61:581–9.
 143. Suga Y, Jarnik M, Attar PS, et al. Transgenic mice expressing a mutant form of loricrin reveal the molecular basis of the skin diseases, Vohwinkel syndrome and progressive symmetric erythrokeratoderma. *J Cell Biol* 2000;151:401–12.
 144. Matsumoto K, Muto M, Seki S, et al. Loricrin keratoderma: a cause of congenital ichthyosiform erythroderma and collodion baby. *Br J Dermatol* 2001;145:657–60.
 145. Ishida-Yamamoto A. Loricrin keratoderma: a novel disease entity characterized by nuclear accumulation of mutant loricrin. *J Dermatol Sci* 2003;31:3–8.
 146. Gray LC, Davis LS, Guill MA. Progressive symmetric erythrokeratoderma. *J Am Acad Dermatol* 1996;34:858–9.
 147. Irvine AD, Paller AS. Molecular genetics of the inherited disorders of cornification: an update. *Adv Dermatol* 2002;18:111–49.
 148. Irvine AD, McLean WH. Human keratin diseases: the increasing spectrum of disease and subtlety of the phenotype–genotype correlation. *Br J Dermatol* 1999;140:815–28.
 149. Terron-Kwiatkowski A, Paller AS, Compton J, et al. Two cases of primarily palmoplantar keratoderma associated with novel mutations in keratin 1. *J Invest Dermatol* 2002;119:966–71.
 150. Terron-Kwiatkowski A, Terrinoni A, Didona B, et al. Atypical epidermolytic palmoplantar keratoderma presentation associated with a mutation in the keratin 1 gene. *Br J Dermatol* 2004;150:1096–103.
 151. Gach JE, Munro CS, Lane EB, et al. Two families with Greither's syndrome caused by a keratin 1 mutation. *J Am Acad Dermatol* 2005;53:S225–30.
 152. Küster W, Zehender D, Mensing H, et al. [Vörner keratosis palmoplantaris diffusa. Clinical, formal genetic and molecular biology studies of 22 families]. *Hautarzt* 1995;46:705–10.
 153. Maestrini E, Monaco AP, McGrath JA, et al. A molecular defect in loricrin, the major component of the cornified cell envelope, underlies Vohwinkel's syndrome. *Nat Genet* 1996;13:70–7.
 154. Lestringant GG, Frossard PM, Adeghate E, et al. Mal de Meleda: a report of four cases from the United Arab Emirates. *Pediatr Dermatol* 1997;14:186–91.
 155. Chimienti F, Hogg RC, Plantard L, et al. Identification of SLURP-1 as an epidermal neuro-modulator explains the clinical phenotype of Mal de Meleda. *Hum Mol Genet* 2003;12:3017–24.
 156. Fischer J, Bouadjar B, Heilig R, et al. Mutations in the gene encoding SLURP-1 in Mal de Meleda. *Hum Mol Genet* 2001;10:875–80.
 157. Perry HO, Su WP. Olmsted syndrome. *Semin Dermatol* 1995;14:145–51.
 158. Lin Z, Chen Q, Lee M, et al. Exome sequencing reveals mutations in TRPV3 as a cause of Olmsted Syndrome. *Am J Hum Genet* 2012;90:558–64.
 159. Madan V, Gupta U. Tyrosinaemia type II with diffuse plantar keratoderma and self-mutilation. *Clin Exp Dermatol* 2006;31:54–6.
 160. Benoldi D, Orsoni JB, Allegra F. Tyrosinemia type II: a challenge for ophthalmologists and dermatologists. *Pediatr Dermatol* 1997;14:110–12.
 161. Natt E, Kida K, Odievre M, et al. Point mutations in the tyrosine aminotransferase gene in tyrosinemia type II. *Proc Natl Acad Sci U S A* 1992;89:9297–301.
 162. Baeta IG, Pereira AC, Guedes AC, et al. Do you know this syndrome? *An Bras Dermatol* 2011;86:605–7.
 163. Dahlqvist J, Törmä H, Badhai J, et al. siRNA silencing of proteasome maturation protein (POMP) activates the unfolded protein response and constitutes a model for KLIICK genodermatosis. *PLoS One* 2012;7:e29471.
 164. Mau U, Kendziorra H, Kaiser P, et al. Restrictive dermopathy: report and review. *Am J Med Genet* 1997;71:179–85.
 165. Smitt JH, van Asperen CJ, Niessen CM, et al. Restrictive dermopathy. Report of 12 cases. Dutch Task Force on Genodermatology. *Arch Dermatol* 1998;134:577–9.
 166. Welsh KM, Smoller BR, Holbrook KA, et al. Restrictive dermopathy. Report of two affected siblings and a review of the literature. *Arch Dermatol* 1992;128:228–31.

167. Navarro CL, De Sandre-Giovannoli A, Bernard R, et al. Lamin A and ZMPSTE24 (FACE-1) defects cause nuclear disorganization and identify restrictive dermopathy as a lethal neonatal laminopathy. *Hum Mol Genet* 2004;13: 2493–503.
168. Navarro CL, Cadiñanos J, De Sandre-Giovannoli AD, et al. Loss of ZMPSTE24 (FACE-1) causes autosomal recessive restrictive dermopathy and accumulation of Lamin A precursors. *Hum Mol Genet* 2005;14: 1503–13.
169. Hamel BC, Happle R, Steylen PM, et al. False-negative prenatal diagnosis of restrictive dermopathy. *Am J Med Genet* 1992;44:824–6.
170. Naveed M, Manjunath CS, Sreenivas V. New manifestations of Neu–Laxova syndrome. *Am J Med Genet* 1990;35:55–9.
171. Abdel Meguid N, Temtamy SA. Neu–Laxova syndrome in two Egyptian families. *Am J Med Genet* 1991;41:30–1.
172. Manning MA, Cunliffe CM, Colby CE, et al. Neu–Laxova syndrome: detailed prenatal diagnostic and post-mortem findings and literature review. *Am J Med Genet A* 2004;125A: 240–9.
173. The Executive and Scientific Advisory Boards of the National Foundation for Ectodermal Dysplasias. Scaling skin in the neonate: a clue to the early diagnosis of X-linked hypohidrotic ectodermal dysplasia (Christ–Siemens–Touraine syndrome). *J Pediatr* 1989; 114:600–2.
174. Courtois G. The NF-kappaB signaling pathway in human genetic diseases. *Cell Mol Life Sci* 2005;62:1682–91.

Immunologic, Reactive, and Purpuric Disorders

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Introduction

In this chapter, a number of non-related entities will be discussed. They appear grouped by convenience, and represent a heterogeneous group of genetic and acquired diseases with a common ground of an immunologic pathophysiology. Several disorders appear to represent hypersensitivity reactions. Purpuric eruptions will also be covered in this chapter. The differential diagnosis of purpura is extensive in neonates and young infants, and includes hematological disorders, infections, trauma, metabolic diseases, and iatrogenic disorders.

Annular erythemas

Annular erythema is a descriptive term that encompasses several entities of unknown etiology characterized by circinate polycyclic lesions that extend peripherally from a central focus.¹⁻³ Because of subtle differences in clinical features, age of onset, duration of individual lesions, and total duration of the eruptions, a variety of descriptive terms have been coined for these disorders (Table 20.1). For prognostic reasons, it is useful to subdivide annular erythemas into transient and persistent forms.⁷ Transient forms include annular erythema of infancy and the less well-established entities erythema gyratum atrophicans transiens neonatale, neutrophilic figurate erythema of infancy and eosinophilic annular erythema. Persistent annular erythemas include erythema annulare centrifugum and familial annular erythema. The most important issue, however, is to exclude entities which require specific evaluation and treatment, such as neonatal lupus, tinea corporis, erythema chronicum migrans, erythema marginatum rheumaticum, erythema gyratum repens, and erythema multiforme. These ‘annular’ erythemas have distinctive clinical or histologic features and are considered below and elsewhere in this book.

ANNULAR ERYTHEMA OF INFANCY

Annular erythema of infancy is a benign disease of early infancy characterized by the cyclic appearance of urticarial papules that enlarge peripherally, forming 2–3 cm rings or arcs with firm, raised, cord-like or urticarial borders.^{4,8} Adjacent lesions become confluent, forming arcuate and polycyclic lesions (Fig. 20.1). Neither vesiculation nor scaling is present at the border. The eruption is asymptomatic. Individual lesions resolve spontaneously without a trace within several days, but new lesions continue to appear in a cyclical fashion until complete resolution within the first year of life. Resolution of the lesions only during febrile episodes has been reported.⁹ A few cases lasting for years have been described.^{10,11}

The cause of annular erythema is unknown, and there are no associated systemic findings. Histologic studies reveal a superficial and deep, dense, perivascular infiltrate of mononuclear cells and eosinophils. No flame figures are observed. The epidermis is normal or mildly spongiotic. Two variants with a predominantly eosinophilic and neutrophilic infiltrate have been described and renamed as *eosinophilic annular erythema* and *neutrophilic figurate erythema of infancy*, respectively.^{9,12}

Laboratory studies are normal. Peripheral eosinophilia does not accompany tissue eosinophilia. Immunoglobulin levels, including IgE levels, are normal. The differential diagnosis should include other annular lesions of infancy (see below). No treatment is warranted because of the self-limited nature of the eruption.

Erythema gyratum atrophicans transiens neonatale is a less well-defined entity,¹³ characterized clinically by annular plaques with an erythematous border and an atrophic center. The lesions appear in the newborn period and resolve within the first year of life. Histologic findings include epidermal atrophy and a mild perivascular mononuclear infiltrate. Immunofluorescence studies reveal granular deposits of IgG, C3, and C4 at the dermoepidermal junction and around capillaries. Erythema gyratum atrophicans transiens neonatale possibly represents a variant of neonatal lupus erythematosus.⁵

ERYTHEMA ANNULARE CENTRIFUGUM

Erythema annulare centrifugum (EAC) is a more persistent type of annular erythema that usually affects adults,¹⁴ but may also occur in children and rarely in newborns.^{7,11,15,16} Two clinicopathologic variants have been identified: a superficial and a deep variety. The lesions consist of annular and polycyclic plaques with an indurated border in the deep variety and a scaly border in the superficial variety. The scales characteristically lag behind the advancing border. Individual lesions resolve spontaneously after a few weeks, but new plaques continue to develop for years, or may be a lifelong condition. There is no associated pruritus. Erythema annulare centrifugum is thought to represent a hypersensitivity reaction to several trigger factors, including infectious agents (*Candida*,¹⁷ Epstein-Barr virus,¹⁶ *Ascaris*,¹⁸ *Pseudomonas*), drugs or foods,^{6,19} and neoplasia, especially in adults. Intradermal injection of candidin or trichophytin may reproduce the clinical lesions.¹⁵

Histologic features for superficial EAC consist of a dense, superficial, perivascular mononuclear infiltrate. There is also parakeratosis or epidermal spongiosis. The deep variant shows a sleeve-like arrangement of the superficial and deep lymphocytic infiltrate, and in some cases of melanophages, subtle vacuolar changes at the dermal-epidermal junction, and individual

TABLE
20.1

Annular erythemas

	Age of onset	Clinical features	Duration of individual lesions	Duration of eruption	Healing	Histopathology
Transient forms						
Annular erythema of infancy ⁴	Early infancy	Annular plaques No scaling or vesiculation Raised borders	Days	Transient (5–6 weeks; cyclic course)	No residual lesions	Perivascular infiltrate of eosinophils
Erythema gyratum atrophicans transiens neonatale	Early infancy	Annular plaques No scaling or vesiculation Raised borders Atrophic center	Days to months	Resolves before first year	No residual lesions	Perivascular monocyctic infiltrate Epidermal atrophy DIF granular IgG; C3 and C4 at the BMZ
Eosinophilic annular erythema	Infants and adults	Annular plaques No scaling or vesiculation Raised borders	Weeks to months	New lesions develop for months or years	No residual lesions	Perivascular infiltrate, very prominent eosinophils, no flame figures
Neutrophilic figurate erythema of infancy	Infants	Annular plaques No scaling or vesiculation Raised borders	Weeks	Cyclic for a few years	No residual lesions	Neutrophils and leukocytoclasia without vasculitis
Persistent forms						
Erythema annulare centrifugum ⁵	Adulthood, newborn period possible	Mild scaling may be seen at borders	Weeks	Persistent (months or years, with new lesions developing continuously)	Residual hyperpigmentation	Superficial and deep perivascular cuff of lymphocytes
Familial annular erythema ⁶	Early infancy to puberty Autosomal dominant	Possible vesiculation or scaling Geographic tongue may be associated Pruritus	Days	Persistent (lifelong, short remissions)	Transient hyperpigmentation	Superficial perivascular cuff of lymphocytes Spongiosis and parakeratosis



Figure 20.1 Annular erythema of infancy. In this case, the eruption was present at birth.

necrotic keratinocytes, which makes differential diagnosis from tumid lupus erythematosus very difficult.^{20,21}

No therapy has been successful in all cases. Depending on the trigger factor, treatment agents that have been used include oral nystatin, oral amphotericin B, topical antifungals, antihistamines, disodium cromoglycate, and interferon- α .^{15,17}

FAMILIAL ANNULAR ERYTHEMA

Familial cases of annular erythema with autosomal dominant inheritance have rarely been described.^{22–24} The onset is in early infancy. Dermographism and pruritus was marked in the original cases. Lesions resolve with residual hyperpigmentation. Chronicity is the rule and geographic tongue may be associated.²³

Differential diagnosis of annular erythemas

Differential diagnosis includes other eruptions with ring-like lesions, such as neonatal lupus, erythema multiforme, urticaria, urticarial lesions of pemphigoid, fungal infections, erythema chronicum migrans, and congenital Lyme disease.^{3,10,25,26}



Figure 20.2 Neonatal lupus with atrophic skin lesions present at birth. (Courtesy of Linda-Beets-Shay, MD.)

Serum antibody determinations (antinuclear, SS-A, and SS-B) are recommended to exclude neonatal lupus. Scraping any scaly lesion for KOH preparation is also advisable.

Neonatal lupus erythematosus

Neonatal lupus erythematosus (NLE)^{27–34} is a disease of newborns caused by maternally transmitted autoantibodies. The major manifestations are dermatologic and cardiac. Skin findings are transient. Cardiac disease, which is responsible for the morbidity and mortality of NLE, begins in utero and affects the cardiac conduction system permanently. Other findings include hepatic and hematologic abnormalities. Mothers of infants with neonatal lupus have anti-Ro/SS-A autoantibodies in 95% of cases. Anti-La/SS-B and anti-U1RNP autoantibodies have also been implicated in the pathogenesis of NLE in a minority of patients.^{35,36}

Cutaneous findings

Of infants with NLE, 50% have skin lesions, and congenital heart block is present in about 10%.^{27,34} Lesions commonly develop at a few weeks of age but may be apparent at birth, which suggests that ultraviolet (UV) radiation is not essential for the development of skin lesions.³⁷ Ulcerations, bullae, and extensive atrophy may be present, particularly in cases that are present at birth³⁸ and transient bullous lesions from severe vacuolar damage of the basal cell layer³⁹ have been reported as unusual manifestations of NLE. These cases might more accurately be called ‘congenital LE’ rather than NLE (Fig. 20.2).

The more common skin manifestations of NLE fall into two main morphologies, papulosquamous and annular. Papulosquamous lesions are more common and are characterized by erythematous, nonindurated scaly plaques (Fig. 20.3), sometimes with an atrophic appearance (Fig. 20.4). In contrast to discoid lupus, scarring and follicular plugging are usually absent. The annular variant consists of well-circumscribed round plaques.⁴⁰ Lupus profundus and generalized poikiloderma with erosions and patchy alopecia are rare manifestations.^{41,42}

NLE lesions are most common on the face and scalp, predominantly affecting the periorbital and malar areas, often causing the ‘racoon eyes’ appearance (Figs 20.4, 20.5), but can occur on virtually any body site. The eruption is frequently



Figure 20.3 Neonatal lupus erythematosus. Annular scaly plaques resembling tinea corporis.



Figure 20.4 Neonatal lupus erythematosus. Atrophic plaques and raccoon eyes on the faces of twins

precipitated or aggravated by sun exposure, but lesions can develop in sun-protected areas (e.g., the diaper region, palms, and soles).^{37,43,44} Skin lesions are transient and cease to appear around the age of 6 months, after the disappearance of maternal antibodies. Transient or persistent hypopigmentation and epidermal atrophy may result (Fig. 20.6).³⁴ Telangiectases, vascular ectasias resembling petechiae, persistent livedo or cutis marmorata, features of cutis marmorata telangiectatica congenita, and widespread erythema mimicking an extensive capillary malformation have been observed but are much less common manifestations. In some cases, these findings can be an initial sign of NLE, occurring without preceding identifiable inflammatory lesions.^{33,45–47} A rare report of a case of NLE with a serological profile consistent with drug-induced lupus has been described in a newborn whose mother was treated with α -interferon during pregnancy.⁴⁸

Extracutaneous findings

The most significant manifestation is isolated complete congenital heart block. More than 90% of such cases are due to



Figure 20.5 Neonatal lupus erythematosus. 'Raccoon eyes' and prominent facial erythema in an infant with neonatal lupus. (Courtesy of Dr Joseph Lam).



Figure 20.6 Neonatal lupus erythematosus. Atrophy and pigmentary changes in an infant with neonatal lupus erythematosus. This boy also had congenital A-V heart block.

NLE. Most patients have third-degree block, but progression from a second-degree block has been reported.⁴⁹ Heart block can often be detected as early as 20 weeks' gestation. Cardiomyopathy and other types of arrhythmias are associated with NLE.⁵⁰

Transient liver disease, manifesting as hepatomegaly (with a picture of cholestasis) or elevation of liver enzymes,^{53,51–53} and thrombocytopenia or other isolated cytopenias, may occur.⁵⁴ Petechiae and purpura have been described as presenting signs of NLE.⁵⁵ Less common findings include thrombosis associated with anticardiolipin antibodies, hypocalcemia, spastic paraparesis, pneumonitis, and transient myasthenia gravis.^{56–58} Central

nervous system (CNS) involvement has been emphasized in some reports, and can be asymptomatic, with only ultrasound and CT scan abnormalities, suggesting a transient phenomenon.⁵⁹ However, hydrocephalus has been reported in 8% of children with NLE.⁶⁰ NLE is a cause of chondrodysplasia punctata, seen in X-rays as stippling of the epiphyses and the spine.⁶⁰ Between 30% and 50% of mothers of infants with NLE have a connective tissue disease, most commonly SLE or Sjögren syndrome. Most, however, are asymptomatic. The risk for developing overt connective tissue disease in these mothers is highly debated, with estimates ranging from 2% to more than 70%.^{34,61–66}

Etiology and pathogenesis

Placentally transmitted maternal IgG autoantibodies are associated with the pathogenesis of NLE.⁶⁷ The most commonly implicated autoantibodies have been anti-Ro/SS-A and anti-La/SS-B, present in 95% and 60–80%, respectively. A small subset of affected infants have neither Ro or La antibodies, but instead have anti-U1RNP.^{35,36} Antibodies against the 52/60-kD Ro and 48-kD La ribonucleoproteins are associated with heart block, whereas antibodies against the 50-kD La ribonucleoprotein are associated with cutaneous disease.⁶⁸ Significantly more symptomatic mothers of children with congenital heart block have anti-La antibodies than do disease-matched mothers with unaffected children.⁶⁹ Moreover, the mean level of anti-La seems to be higher in mothers of infants with congenital heart block than in mothers of children with cutaneous NLE.⁷⁰ It is likely that the amount of maternal antibodies, rather than their presence, is associated with fetal injury.⁶⁸

Why less than 5% of mothers with anti-Ro and anti-La antibodies give birth to affected children is not understood, nor is the fact that mothers of affected infants are often asymptomatic despite having these antibodies. Fraternal twins are often discordant for NLE, and NLE does not occur in every subsequent pregnancy. Genetic factors may be important for the development of NLE in children with maternal lupus antibodies. A link has been suggested between NLE rash and the allele HLA-DRB1*03, as well as a -308A polymorphism in the TNF- α gene.³² Alternatively, maternal and/or sibling microchimerism may play an additional role, as levels of microchimerism have been reported to correlate with NLE disease activity.⁷¹

Laboratory tests and histopathology

Serologic studies for autoantibodies in the mother and infant demonstrate anti-Ro, anti-La, and/or anti-U1RNP antibodies. Anti-NDNA, anticardiolipin antibodies, antinuclear antibody, and rheumatoid factor may also be present. Anti-Sm antibody, highly specific for systemic lupus erythematosus, is not found in NLE. The maternal antibody titer is usually higher than the infant titer. In apparently seronegative infants, more sensitive studies such as ELISA, immunoblotting, or line immunoassay, should be used instead of immunodiffusion techniques. Skin biopsy, which is usually not necessary for diagnosis, shows changes characteristic of lupus erythematosus, i.e., epidermal atrophy, vacuolization of the basal layer with a sparse lymphohistiocytic infiltrate at the dermoepidermal junction with a periappendageal distribution. In many instances, histopathological features in children with NLE rash are subtle. Direct immunofluorescence is positive in 50% of cases, demonstrating granular deposits of IgG, C3, and IgM at the dermoepidermal junction.

Differential diagnosis

The differential diagnosis encompasses congenital infections including rubella, cytomegalovirus and syphilis, congenital graft-versus-host disease, annular erythema of infancy, tinea corporis, and seborrheic dermatitis. False-positive VDRL tests for syphilis may occur in NLE. Telangiectasia and photosensitivity may suggest Bloom syndrome or Rothmund–Thomson syndrome. Serologic studies for autoantibodies in both infant and mother help to confirm the diagnosis. Skin biopsy for histologic and direct immunofluorescence studies is seldom necessary.

Course, management, treatment, and prognosis

Neonates with suspected NLE should receive a complete physical examination, electrocardiogram, complete blood count with platelet count, and liver function tests (Box 20.1).

Skin lesions are transient. Treatment of skin disease consists of sun protection and the application of topical steroids. Pulsed dye laser therapy may be considered for residual telangiectasia. Congenital heart block is permanent. Half of newborns with complete congenital heart block require implantation of a pacemaker in the neonatal period.^{30,64,72} The average mortality rate from complete congenital heart block in the neonatal period is 15%; another 10–20% die of pacemaker complications.^{25,30} Late-onset cardiomyopathy may develop in a few infants.^{73–75}

Mothers with anti-Ro or anti-La antibodies have a risk of delivering an infant with NLE in the range of 1–20%, depending on whether they have asymptomatic or symptomatic SLE.^{27,30} The risk of recurrence of congenital heart block in subsequent pregnancies may be as high as 25%.⁶⁴ Such pregnancies should be closely monitored, ideally by obstetricians familiar with managing high-risk pregnancies. Although NLE is usually self-limited, SLE or other rheumatologic/autoimmune diseases may develop later in life in a small subset of patients.^{65,76,77} The exact risk is unknown.

Other collagen vascular disorders of the newborn and young infant

Collagen vascular disorders seldom appear in newborns and young infants. Both discoid and systemic lupus erythematosus (LE) has been reported in infants below 12 months of age, but skin lesions are very unusual.^{78–81} A systemic LE-like rash was seen at 12 months of age in an infant with C1q deficiency.⁸²

BOX 20.1 RECOMMENDED EVALUATION OF CHILDREN WITH NEONATAL LUPUS ERYTHEMATOSUS

- Clinical skin examination
- Complete clinical examination
- Skin biopsy (if clinical diagnosis not achieved)
- Full blood count (including platelets)
- Coagulation screen (including lupus anticoagulant and antiphospholipid antibodies)
- Serum chemistry (including liver function test)
- Autoantibody screening: antinuclear antibodies, anti-Ro, anti-La, anti-RNP
- Electrocardiogram and echocardiogram. Referral to pediatric cardiologist
- CNS ultrasound. Consider brain CT scan or MRI if clinical examination abnormal

Patients with familial chilblain lupus have been reported to develop skin lesions in infancy. Familial chilblain lupus is usually due to mutations in the *TREX1* gene, and thus is allelic with the Aicardi–Goutières syndrome (AGS).⁸³ In AGS, chilblains are a common symptom, and there is some overlap between AGS and familial chilblain lupus. In one family, a dominant heterozygous mutation in *SAMHD1* caused familial chilblain lupus with infantile onset.⁸⁴

Localized (linear) morphea can be present at birth, but this is very rare.⁸⁵ It may be initially confused with vascular malformations such as port-wine stains.

Drug eruptions

Cutaneous drug reactions^{86,87} are very rare in neonates. This is likely due to the relative inability to generate a drug-induced immune response^{88–90} and the lack of medication exposures together with time lag for sensitization required in many drug hypersensitivities. However, drug eruptions become far more common in older infants. These eruptions may be true hypersensitivity reactions, but many are idiosyncratic reactions, triggered in the setting of concomitant viral illnesses. If a drug eruption is suspected, a detailed history of medications should be obtained. In breast-feeding infants, this should include medications taken by the mother. A history of recent vaccinations can also be relevant.

Maculopapular and morbilliform eruptions are the most frequent type of drug reactions in infants and usually have a benign course (Fig. 20.7). These eruptions are characterized by the abrupt onset of multiple small pink-red macules and papules that begin on the head and upper trunk and symmetrically progress downwards (Figs 20.8, 20.9). The lesions appear within the first 2 weeks of starting the offending medication and are often pruriginous. Most benign drug reactions are delayed-type hypersensitivity reactions to antibiotics.⁹¹ Distinguishing a drug eruption from a viral exanthem is often difficult. Skin biopsy is not helpful in most cases. It has been proposed that FAS ligand serum concentration might be useful in discriminating between drug rashes and viral exanthems, as it is raised in drug reactions and consistently low in viral



Figure 20.7 Extensive erythematous eruption caused by a systemic antibiotic.



Figure 20.8 Drug eruption resulting from procainamide.



Figure 20.9 Maculopapular eruption caused by diazoxide.

rashes,⁹² but it is not available in most clinical settings. Drug eruptions are usually self-limiting after prompt recognition and discontinuation of the causative drug. Antihistamines in infants older than 6 months of age may help to alleviate the pruritus, but systemic steroids are not indicated unless the reaction is severe, and their efficacy remains controversial. Drug rechallenge to confirm the diagnosis is not recommended,⁹¹ and family education about generic and trade drug names is important to avoid recurrences.

The primary infection by Epstein–Barr virus (EBV), usually asymptomatic in young children, may display the so-called ‘ampicillin rash’ when patients are given ampicillin, amoxicillin or, much less frequently, other antibiotics such as cephalosporins or macrolides. The incidence of ampicillin rash in EBV infection was estimated to appear in 90% of patients, but recent studies have shown that the amoxicillin-induced rash appears only in about 30% of cases.⁹³ The antibiotic-related rash can be macular, petechial, scarlatiniform or urticarial, and it can be differentiated from the spontaneous eruption in EBV infection in that it begins 1–2 days after starting the antibiotic treatment and that it is more severe and generalized, involving the head, neck, trunk, extremities, and even palms and soles. No consistent relationship has been shown for antibiotic dose,

duration of treatment, atopic history, or previous exposure to penicillin. The pathogenesis behind the aminopenicillin-associated rash is uncertain. Ampicillin and amoxicillin can be re-administered after viral resolution without any adverse effect, suggesting a toxic etiology and not a true allergy.^{93,94}

Vancomycin, an antibiotic frequently administered to premature newborn infants for *Staphylococcus epidermidis* nosocomial infections, may produce shock and rash (red-baby syndrome).^{95,96} This reaction is characterized by the appearance of an intense, macular, erythematous eruption on the neck, face, and upper trunk shortly after the infusion is completed. It may be accompanied by hypotension and shock. The reaction resolves rapidly in a matter of hours. It is frequently associated with rapid infusion; however, lengthening the infusion to more than 1 hour does not completely eliminate the risk.

Newborns with AIDS have an increased susceptibility to drug reactions.^{97,98} Reactions to trimethoprim/sulfamethoxazole in patients with HIV infections can be severe and life-threatening.⁹⁹

Fixed drug eruptions (FDE) are rare in infants and newborns. The classic cutaneous reaction of FDE consists of one or more round, well-circumscribed, erythematous to violaceous patches of variable size that appear anywhere on the body. Trimethoprim-sulfamethoxazole and non-steroidal anti-inflammatory drugs are well-known causes of fixed drug eruptions. Reactions of the scrotum and penis, with erythema and edema resulting from hydroxyzine hydrochloride, have also been described in early infancy,¹⁰⁰ as well as bullous forms.¹⁰¹ Recurrences in the exact same location are common prior to diagnosis.

Vegetant bromoderma is a reaction to bromides characterized by coalescing papules and pustules which form vegetant inflammatory or pseudotumoral lesions. It usually affects the scalp, face, and legs. Most cases of vegetant bromoderma have been described in infants after the ingestion of syrups and solutions containing bromide, which has sedative, anticonvulsant and expectorant properties, or the spasmolytic agent scopolamine bromide.^{102,103} The eruption ceases after withdrawal of bromide. The risk of systemic intoxication, known as bromism, makes it advisable to avoid bromide use in newborns and infants.

Other anecdotal reports of toxicoderma in very young infants or newborns have been described, such as a papular eruption from G-CASF for collection of stem cells,¹⁰⁴ a lichenoid reaction to ursodeoxycholic acid for neonatal hepatitis,¹⁰⁵ and a maculopapular rash from diazoxide used for neonatal hyperglycemia (Fig. 20.9).¹⁰⁶

Serum sickness-like reaction is rare in neonates but has been reported in infants as young as 5 months of age.¹⁰⁷ It is characterized by fever, an urticarial eruption, and arthralgias. Lymphadenopathy may be present. In contrast to true serum sickness, there are no immune complexes, vasculitis, or renal impairment. The most commonly implicated drug has been cefaclor,^{107–109} but this eruption can be seen in infants with an unknown or presumably viral etiology (Fig. 20.10).

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis (AGEP) is characterized by acute onset of fever and a widespread eruption of less than 5 mm sterile pustules on an erythematous background

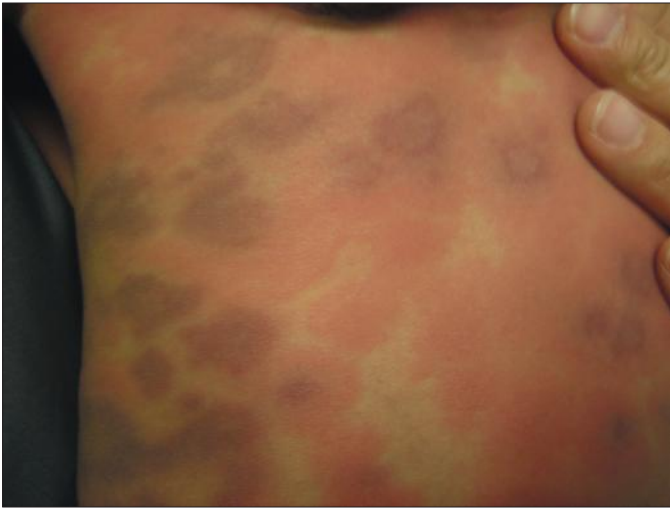


Figure 20.10 Infant with serum sickness-like eruption.



Figure 20.11 Acute generalized exanthemic pustulosis. Background erythema and coalescing pustules are characteristic findings. (Courtesy of Scott Norton, MD.)

(Fig. 20.11). It is more common in older children and adults, but a few cases have been reported in infancy.^{110,111} Known etiologies of AGEPS include exposure to systemic medications, mainly antibiotics, recent viral infection, vaccinations,¹¹¹ and exposure to mercury.¹¹² Histological study shows subcorneal pustules associated with dermal edema, and occasionally vasculitis, eosinophils in the superficial dermis, and focal keratinocyte necrosis. AGEPS may be both clinically and histologically difficult to distinguish from pustular psoriasis. In AGEPS, however, additional skin lesions such as purpura, vesicles, bullae, and target lesions, may be seen,^{111,112} there is an antecedent drug exposure in most cases, and the fever and pustules have a shorter duration than in pustular psoriasis. The condition fades away in a few days to weeks after abandoning the offending medication.

DRUG-INDUCED HYPERSENSITIVITY SYNDROME

Drug-induced hypersensitivity syndrome (DISH), also known as ‘drug reaction with eosinophilia and systemic symptoms’

(DRESS) is a serious drug reaction characterized by fever, skin rash, lymphadenopathy, hematological abnormalities and internal organ involvement, especially involving the liver.^{113–115} It is rare in this age group, although a fatal case in a 3-month-old infant has been reported, as well as a case in a premature infant,^{116,117} and another in a 22-month-old patient.¹¹⁸ The most commonly implicated drugs are anticonvulsants, particularly phenobarbital, phenytoin, carbamazepine, and lamotrigine, and antibiotics, e.g., trimethoprim-sulfamethoxazole, isoniazid, vancomycin, and amoxicillin.¹¹⁹ It usually occurs within 2 months of the introduction of the offending drug, most often in 2–6 weeks, but cases developing after 3 months of exposure have also been reported.¹²⁰ However, symptoms can appear earlier and be more severe after re-exposure. The condition may be progressive even after discontinuation of the causative agent. Affected patients are frequently initially misdiagnosed as having less severe conditions such as streptococcal pharyngitis, mononucleosis, or other viral illness, both because the association with medication is not recognized and because early cutaneous manifestations are nonspecific maculopapular rashes. Facial and periorbital swelling are very characteristic and suggestive of DRESS. Diffuse erythroderma, desquamation and occasionally vesicles and bullae evolving into Stevens–Johnson syndrome or toxic epidermal necrolysis may occur (Table 20.2).¹²¹ Erythema multiforme-like targetoid lesions and features mimicking Kawasaki disease (KD) have been reported.^{119,122} In addition to the nearly universal fever, rash and lymphadenopathy, laboratory abnormalities are common, namely eosinophilia, atypical lymphocytosis and elevated transaminases. Lungs, kidneys, muscle, and the gastrointestinal system may also be affected.¹²³ Thyroid disease has been reported in 6–10% of pediatric patients.^{120,123} Systemic steroids are the most commonly used therapy,^{113,114,123} and successful treatment with intravenous immunoglobulins in refractory-to-steroid cases has also been reported.¹²⁴ Although the prognosis is generally good, the condition is potentially life-threatening and early diagnosis and discontinuation of the offending drug are very important. In cases of severe cutaneous or systemic involvement, admission to an ICU or a burn unit for careful monitoring is mandatory (Box 20.2).¹²⁵

Stevens–Johnson syndrome and toxic epidermal necrolysis

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are characterized by detachment of epidermis, acute skin blisters, and mucous membrane erosions, and are generally considered to be on a spectrum of the same disease. SJS is defined as epidermal detachment of <10% body surface area (BSA), TEN as >30% BSA involvement, and cases with 10–30% BSA classified as SJS/TEN overlap.¹²⁶ All forms are extremely rare in newborns and very infrequent in infants.

Cutaneous findings

Cutaneous involvement is widespread but usually involves the trunk and consists of flat targetoid lesions with two zones of erythema or ill-defined confluent flat erythematous to purpuric macules.¹²⁷ Underlying erythema and blisters may be seen in both presentations (see Fig. 10.34). Mucosal erosions are reported to be present in more than 90% of patients, and a majority have two or more affected membranes^{127,128} with oral and conjunctival mucosa most commonly affected, and less

TABLE
20.2

Characteristic findings of severe cutaneous drug reactions

	DRESS	SJS/TEN	AGEP
Onset of eruption	2–6 weeks	1–3 weeks	48 h
Duration of eruption (weeks)	Several	1–3	<1
Fever	+++	+++	+++
Mucocutaneous features	Facial edema, morbilliform eruption, pustules, exfoliative dermatitis, tense bullae, and possible target lesions	Bullae, atypical target lesions, and mucocutaneous erosions	Facial edema, pustules, tense bullae, possible target lesions, and possible mucosal involvement
Histological pattern of skin	Perivascular lymphocytic infiltrate	Epidermal necrosis	Subcorneal pustules
Lymph node enlargement	+++	–	+
Hepatitis	+++	++	++
Other organ involvement	Interstitial nephritis, pneumonitis, myocarditis, and thyroiditis	Tubular nephritis and tracheobronchial necrosis	Possible
Neutrophils	↑	↓	↑↑↑
Eosinophils	↑↑↑	–	↑
Neutrophils	↑	↓	↑↑↑
Mortality rate	10%	5–35%	5%

AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Modified from Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part II. Management and therapeutics. *J Am Acad Dermatol* 2013; 68(5):709.e1–e9.

BOX 20.2 MANAGEMENT OF SEVERE DRUG REACTIONS

1. Immediate discontinuation of any possible offending drugs and directed search for evidence of triggering infections
2. Analytical assessment at admission: CBC, LFT, BMP, creatinine, BUN, urinalysis, CPK, LDH, ferritin, triglycerides, calcium, sodium, potassium, coagulation tests, TSH, PTH, lipase, CRP, ANA, quantitative PCR for HHV6, HHV7, EBV, and CMV
3. Supportive care in a skilled unit (e.g., ICU/burn unit) if extensive cutaneous involvement or laboratory abnormalities
 - Appropriate room temperature (30–32°C)
 - Analgesia (avoid NSAIDs)
 - Fluid and electrolyte imbalance
 - Caloric replacement (enteral/parenteral nutrition)
 - Conservative management of wounds, without debridement
 - Appropriate wound dressing to avoid superinfections (use non-adhesive dressings, avoid topical sulfonamide-containing medications; if extensive involvement, consider biosynthetic skin equivalents)
 - Ophthalmologist consultation for eye care
 - Oral antacids and mouth care
 - Surveillance of sepsis and secondary infections with periodic cultures of skin exudates, sputum and eye/mouth secretions
 - Treatment of superinfections and bacteremias
 - Physical therapy to prevent pulmonary involvement and joint contractures
4. Consult the appropriate specialists to manage complicated ocular and visceral involvement
5. Use of systemic therapy and immunosuppressive therapy is still controversial in SJS/TEN but systemic steroid therapy is widely accepted in DRESS syndrome with significant systemic involvement

ANA, antinuclear factor; BMP, basic metabolic panel; BUN, blood nitrogen urea; CBC, complete blood count; CMV, cytomegalovirus; CPK, creatine phosphokinase; CRP, C-reactive protein; EBV, Epstein–Barr virus; HHV, human herpes virus; LDH, lactate dehydrogenase; LFT, liver function tests; PTH, parathyroid hormone; TSH, thyroid stimulating hormone.



Figure 20.12 Oral mucosal involvement in Stevens–Johnson syndrome

frequently genital, anal, pharyngeal, and upper respiratory tract involvement developing (Fig. 20.12; Box 20.1). Numerous reports have described patients with ‘atypical SJS’ who were infected with *Mycoplasma pneumoniae* and presented with severe mucositis without skin lesions.¹²⁹

Extracutaneous findings

SJS and TEN patients are febrile with malaise and constitutional symptoms. In cases of extensive involvement, an elevated sedimentation rate, leukocytosis, and mild elevation of transaminases may be seen, as well as eosinophilia in drug-related cases. Electrolyte imbalance and hypoproteinemia may be encountered in SJS.

Etiology and pathogenesis

Both SJS and TEN are considered to be immune-mediated mucocutaneous reactions, usually secondary to medications or infections. *Mycoplasma pneumoniae* infection is a well-

documented cause.^{130,131} In children, the majority of cases are triggered by anticonvulsants, sulfonamides, and oxicam nonsteroidal anti-inflammatory drugs.^{132,133} Cases of TEN in newborns due to *E. coli* sepsis have been reported; other cases have been related to antibiotics and phenobarbital.¹³⁴ The greatest risk of development of SJS occurs during 7–21 days after a medication has been started.¹³² Other reported triggers of SJS include immunizations and viral infections, and as an acute manifestation of graft-versus-host disease in infants with severe combined immunodeficiency or after bone-marrow transplantation.¹³⁵

Histopathology

Skin biopsy reveals a superficial perivascular mixed infiltrate with vacuolar interface change and apoptotic keratinocytes progressing to full-thickness epidermal necrosis in TEN.

Differential diagnosis

The main differential diagnosis in cases with severe mucosal involvement is erythema multiforme (EM), which is most often triggered by herpes simplex virus infection (see below).^{126,128,136} Staphylococcal scalded skin syndrome (SSSS) can also resemble SJS, particularly early SJS, but the lack of intraoral involvement and level of blistering are helpful clues to differentiate the two conditions.

Treatment

SJS and TEN are potentially life-threatening conditions and their clinical course is typically prolonged, even after drug discontinuation. There is no evidence-based standardized treatment other than supportive care (Box 20.2). Therapies such as systemic corticosteroids and intravenous immunoglobulin, alone or in combination,^{137–139} are often used but are controversial.¹⁴⁰ Recurrences have been reported in up to 20% of patients, a high rate that strongly suggests a potential genetic predisposition.¹³⁹ Such mechanisms have been shown in Asian patients with the HLA-B*1502 genotype, who have a strong tendency to develop carbamazepine-induced SJS.¹⁴¹ *Mycoplasma pneumoniae*-induced SJS has a better prognosis than its drug-induced counterpart.^{128,130} Long-term sequelae due to genital and ocular scarring may impact the long-term prognosis.^{128,139}

Erythema multiforme

Erythema multiforme (EM) is an acute, self-limited disorder of skin and mucous membranes.^{142–144} It was previously classified as EM minor and EM major, depending on whether there was one or more mucous membranes involved respectively, and the term EM major was often used synonymously with SJS. However, there is now evidence that EM and the spectrum of SJS/TEN have distinct clinical features and different precipitating factors, so the terms ‘EM major’ and ‘EM minor’ are best avoided.^{127,145} EM is a common disease in children but extremely unusual in the neonatal period and rarely occurs during infancy.^{97,143,146–151}

Cutaneous findings

The prototypic lesion of EM is a 1–3 cm targetoid lesion with a dusky vesicular, purpuric, or necrotic center surrounded by a raised edematous ring of pallor and an erythematous outer ring. In some cases, only two zones are seen, with a single ring around the central papule (atypical target lesions). The lesions are distributed symmetrically on the extensor surface of the



Figure 20.13 Target lesions of erythema multiforme in a newborn.

extremities and acral parts of the body (Fig. 20.13). They may extend to the trunk, flexural surfaces, palms, and soles. In children, lesions on the face and ears are common, but are rare on the scalp.¹⁵² Areas of epidermal detachment may occur, but usually affect less than 10% of the body surface area. Mucosal lesions may occur in EM but are usually milder than in SJS.

Extracutaneous findings

Mild, nonspecific, prodromal symptoms of cough, rhinitis, and low-grade fever are occasionally present in EM.

Etiology and pathogenesis

EM has been considered a hypersensitivity reaction to multiple precipitating factors such as infectious agents, medications, or even severe contact dermatitis. In children, herpes simplex infections are thought to be responsible for more than 80% of EM, although clinical infection may be minor or inapparent.¹⁵³ HSV-associated EM follows the lesions of herpes by 1–3 weeks. It can recur but not necessarily with every episode of HSV infection. HSV-specific DNA has been detected by polymerase chain reaction and in situ hybridization in lesional skin from children with EM, whether ‘idiopathic’ or clearly HSV-related.¹⁵³ Cow’s milk intolerance has been described as a cause of erythema multiforme in a neonate.¹⁴⁸ Vaccinations were the only known possible causative agents in a newborn and two infants with erythema multiforme.^{150,154}

Laboratory tests and histopathology

The diagnosis is generally made clinically. Histopathologic examination of early lesions reveals a lymphocytic band-like infiltrate at the dermoepidermal junction, with exocytosis and individual necrotic keratinocytes in close proximity to lymphocytes (‘satellite cell necrosis’). There is vacuolization of the basal layer with focal cleft formation at the dermoepidermal junction. The upper dermis is edematous. Over time, more extensive confluent necrosis of the epidermis supervenes, resulting in subepidermal blister formation.

Differential diagnosis

The most common mimic of EM is urticarial multiforme or serum sickness-like reactions (see below). Others include urticarial vasculitis, acute hemorrhagic edema of infancy, Kawasaki disease, EM-like drug eruptions, and Stevens–Johnson syndrome (Table 20.3).

TABLE
20.3

Differential diagnosis of erythema multiforme and STS/TEN

	Erythema multiforme	SJS/TEN
Lesion morphology	Raised three-zone targets	Flat atypical two-zone targets and macules
Mucosal involvement	Milder	More severe
Percent epidermal detachment	<10%	10–30%
Distribution	Acral and extremities	Widespread and truncal
Underlying erythema	Localized	Diffuse
Underlying disease	Uncommon	Common
Recurrences	Common	Uncommon
Etiology	HSV or other infections, rarely drugs	Drugs (less commonly secondary to infection)



Figure 20.14 Generalized urticaria following DPT and polio immunizations.

Course, management, treatment, and prognosis

Erythema multiforme is usually self-limited. Individual lesions heal in 1–2 weeks, with residual hyperpigmentation. Conservative supportive care is the preferred form of treatment. Possible underlying causes should be sought and treated. Corticosteroids are usually unnecessary and may even worsen a concurrent infection.^{155,156} In HSV-associated EM, early intervention or even prophylactic treatment with oral acyclovir may be beneficial.¹⁵⁷

Urticaria and urticarial eruptions

Urticaria (hives) and urticarial lesions (other conditions with hive-like morphology) occur frequently in childhood but are uncommon in children younger than 6 months and even rarer in the neonatal period.^{86,158–167}

Urticaria is defined by the development of transient edematous pruritic wheals (Fig. 20.14). By definition, individual

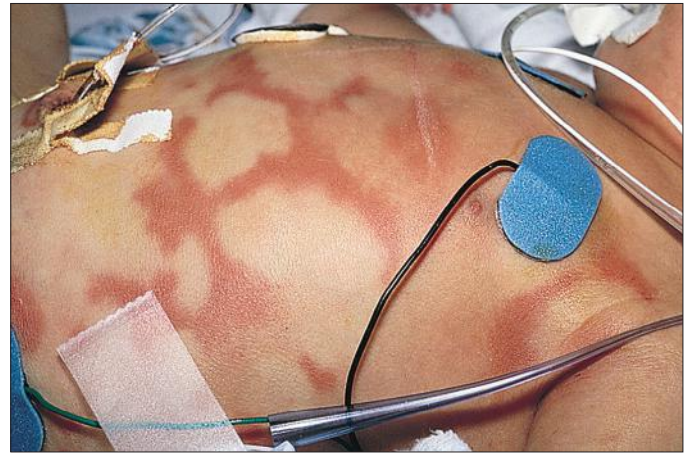


Figure 20.15 Polycyclic lesions of urticaria associated with prostaglandin E_2 infusion.

lesions last less than 24 hours. Hives may occur on the skin and mucous membranes. Urticaria is usually sporadic; however, familial forms with autosomal dominant inheritance have been described for certain forms of urticaria including many of the physical urticarias, such as dermatographism, heat urticaria, cold urticaria, vibratory urticaria, and familial hereditary angioedema.

Urticaria and urticarial eruption may be seen in different clinical situations and can be classified in acute and chronic urticaria, physical urticarias and urticarial eruptions with systemic symptoms or in the context of a systemic or autoinflammatory disease depending on disease duration, triggers, associated diseases, and prognosis.

ACUTE AND CHRONIC URTICARIA

Urticaria can be divided into acute (lasting <6 weeks) and chronic (lasting >6 weeks) types. This division, while somewhat arbitrary, has prognostic and etiopathogenic significance. Chronic urticaria is very rare in infancy and suggests the possibility of an underlying systemic disease.^{160,168,169}

Physical urticarias represent a special subgroup of urticaria in which wheals are elicited by different types of physical stimuli.¹⁷⁰ These include dermatographic, cold, pressure, cholinergic, aquagenic, vibratory, and solar urticaria.

Cutaneous findings

Urticaria is characterized by transient pruritic wheals that in younger children, may have certain characteristic features. Itching may be absent and may be replaced by pain in this age group. The hives tend to coalesce, forming bizarre polycyclic, serpiginous, or annular shapes (figurative urticaria, Fig. 20.15; or annular urticaria, Fig. 20.16), and may become hemorrhagic.^{158,161} The term ‘urticaria multiforme’ has been coined to describe this form of annular urticaria, as it is often confused with erythema multiforme, especially in cases where there is an ecchymotic dusky center.¹⁷¹ Sometimes there may be purpura or ecchymosis in urticaria multiforme and the term ‘hemorrhagic urticaria’ has been coined for this. In these cases, the purpura persists longer than 24 hours but the erythematous edematous plaques change from area to area. These features confer a very dramatic appearance to the eruption.



Figure 20.16 Annular urticaria of unknown etiology.

Urticaria multiforme may be also confused with serum sickness-like reaction because there is often associated facial, hand, and feet edema (angioedema). However, in serum sickness-like reaction, often triggered by antibiotics, there may be accompanying fever and arthralgias.

Extracutaneous findings

Acute urticaria may be accompanied by signs of anaphylactic shock. Urticaria may have associated angioedema with a deep swelling of the face, extremities and genitalia, as well as abdominal pain, diarrhea, vomiting, respiratory compromise, and joint pain. Chronic urticaria in children may be the first presenting sign or be seen in autoimmune disorders such as thyroid autoimmunity, systemic lupus, or juvenile arthritis.

Etiology and pathogenesis

In conventional urticaria, hives develop as a result of an increased permeability of capillaries and small venules, which leads to leakage of fluid into the extravascular space.^{86,162} Mast cell activation leads to release of mediators, such as histamine, that are responsible for these changes. Many triggers (secretagogues) initiate mast cell degranulation through receptors on mast cell membranes, either via an IgE-dependent mechanism or through complement activation (immunologic secretagogues), or by acting directly without the need for receptors (nonimmunologic secretagogues).

The most common provocative agents of acute urticaria in children are infections, drugs, and foods, which account for 40% of the cases of acute urticaria.^{161,164,166} In the majority of cases of urticaria in children, there is a history of upper respiratory tract infection, otitis media or viral symptoms preceding the onset and many infectious agents have been reported, including mycoplasma, group A *Streptococcus*, adenovirus, herpes virus type 6, parvovirus, *Helicobacter pylori*, and others.¹⁶⁷ However, exhaustive diagnostic evaluations for an infectious etiology are generally not helpful unless directed by other signs or symptoms. Antibiotics (penicillins, macrolides, and oral cephalosporins), anticonvulsants and NSAIDs are the most frequently incriminated drugs. In IgE, mediated food allergy hives usually appear within minutes to 2 hours after ingestion, and respiratory, gastrointestinal and/or cardiovascular signs and symptoms may also be present. In infants, cow's milk is the most common food for food-induced urticaria and anaphylaxis.

Urticaria may be more common and recurrent in atopic patients.^{161,164}

Identifying the cause of chronic urticaria is even more difficult as it is often idiopathic. Occult infections should be considered (such as a low-grade urinary tract infection or otitis), as well as autoimmune disorders. Thyroid autoimmunity, juvenile idiopathic arthritis, systemic lupus erythematosus, type 1 diabetes, and coeliac disease have been associated with chronic urticaria in children, but not in infants.¹⁶⁹

Diagnosis

The diagnosis of urticaria is usually made clinically. In atypical or chronic cases, skin biopsy may be helpful, particularly if persistent or if prominent systemic symptoms are present. Histopathologic examination demonstrates vascular dilation, edema, and a perivascular inflammatory infiltrate most typically composed of lymphohistiocytic cells, polymorphonuclear cells, and eosinophils. The presence of neutrophils, particularly if predominant, can be an important clue to an autoinflammatory disease, which requires different evaluation and management (see below).

In most cases, laboratory tests are not usually necessary to evaluate acute urticaria, unless signs point to a specific infection. An exhaustive search for an underlying cause not elicited by history alone is unwarranted. In drug-induced urticaria, the eosinophil count may be elevated. In cases with recurring episodes, it may be useful to keep a diary of triggering factors. In many patients, no cause is identified. For chronic urticaria the same principles apply and investigation of thyroid autoimmunity, celiac disease and other autoimmune conditions may be considered if suggested by the patient's history or signs.

Differential diagnosis

Urticaria in infants is often misdiagnosed as erythema multiforme, acute hemorrhagic edema and other forms of vasculitis, annular erythema of infancy, Kawasaki disease, or serum sickness. In neonates, generalized hive-like eruptions and dermatographism can also be seen in diffuse cutaneous mastocytosis (see [Chapter 28](#)).¹⁷² Hemorrhagic urticaria and annular urticaria especially may be mistaken for erythema multiforme because the dusky center gives a targetoid configuration ([Table 20.4](#)). However in urticaria, there are no epidermal changes, blistering, or necrotic centers. Autoinflammatory conditions should always be considered in the differential diagnosis of neonates with urticaria, especially in febrile infants (see below).

Course, management, treatment, and prognosis

Acute urticaria in infants is usually benign and self-limiting. If medication is required, oral antihistamines are the mainstay of therapy. First generation antihistamines are safe in older infants, however, in newborns who have an increased susceptibility to antimuscarinic side-effects, they may cause central nervous system (CNS) excitation, which in rare cases can lead to seizures. Second generation antihistamines such as cetirizine and levocetirizine have been proved to be safe in infants older than 6 months.^{173,174} Systemic corticosteroids are rarely necessary.

PHYSICAL URTICARIAS

Physical urticarias represent a subset of urticaria triggered by physical agents. These include cold, cholinergic (heat), solar, dermatographic, delayed-pressure, and vibratory urticaria.

TABLE
20.4

Differential diagnosis of urticaria multiforme and erythema multiforme

	Skin lesions	Duration of individual lesions	Mucous membranes	Angioedema (face and extremities)	Dermographism	Pruritus	Triggers	Treatment
Urticaria multiforme	Annular and polycyclic wheals with central clearing	24–36 h, no fixed lesions. No residual pigmentation	Swollen lips and mucosal edema may be present without erosions	May be present	May be present	Present	Viral infections, drugs, idiopathic	Discontinue any new or unnecessary medications; antihistamines; systemic steroids can be helpful in more recalcitrant cases
Erythema multiforme	Annular and polycyclic papules and plaques with necrotic, vesicular or dark center, middle ring of pallor and edema, outer ring of erythema or blisters	7–10 days, fixed lesions. Residual pigmentation	Blisters and erosions may be present	Not present	Not present	Usually mild	Herpes virus, mycoplasma	Supportive care; early institution of systemic steroids can sometimes be helpful

Adapted from Shah KN, Honig PJ, Yan AC. 'Urticaria multiforme': a case series and review of acute annular urticarial hypersensitivity syndromes in children. *Pediatrics* 2007 May; 119(5):e1177–83.

Physical urticarias are often chronic. Dermographism is the most common type.

Dermographism is manifested by the appearance of linear wheals at the sites of rubbing or scratching of the skin. Wheals usually fade in a few minutes. It is the most common form of physical urticaria in young children and in many cases of ordinary acute and chronic urticaria, there is some degree of dermographism. In neonates, dermographism can also be a manifestation of 'silent' diffuse cutaneous mastocytosis.¹⁷²

In pressure urticaria, deep painful wheals develop at sites of the pressure. The onset of the urticarial lesions may be delayed for a few hours after the pressure.

Cholinergic urticaria is characterized by discrete, small, papular wheals elicited by heat, stress, or physical activity. Aquagenic urticaria is considered a variant of cholinergic urticaria triggered by contact with water or perspiration independent of temperature. Both are usually seen in adolescents and adults.

Acquired cold urticaria is triggered by contact with cold objects, water or air. It is the most severe form of all the physical urticarias, as it may be associated with angioedema, hypotension and syncope. Acquired cold urticaria may be primary or secondary to cryoglobulinemia or a viral infection.

Familial forms with autosomal dominant inheritance have been described for dermographic, vibratory, cholinergic, and cold urticaria.^{175–177} Although rare, these familial cases begin early in life, even immediately after birth, and have a lifelong course, usually with increased severity. Familial cold urticaria is discussed below within the autoinflammatory syndromes.¹⁷⁸

URTICARIAL ERUPTIONS ASSOCIATED WITH AUTOIMMUNE DISORDERS OR AUTOINFLAMMATORY DISEASES

Autoimmune diseases such as thyroid autoimmunity, juvenile idiopathic arthritis, systemic lupus erythematosus, type 1 diabetes, and coeliac disease have been associated with chronic urticaria but this is extremely unusual in infants. In many cases, there are other symptoms and signs that point to the correct diagnosis.

In neonates and infants, urticarial eruptions, especially if persistent, can be the first manifestation of cryopyrin-associated periodic syndromes (CAPS) such as NOMID and familial cold urticaria. In NOMID, the urticarial eruption is usually not pruritic, is very persistent, and often there is associated fever. The other symptoms of NOMID such as arthropathy and neurologic symptoms develop soon after. Familial cold urticaria may present in infancy or early childhood with urticaria induced by cold exposure but characteristically there is delayed onset after exposure. Fever and arthralgia are often present.

ISOLATED ANGIOEDEMA

Angioedema is characterized by subcutaneous edema, with diffuse swelling of the eyelids, genitalia, lips, and tongue. Angioedema is most commonly seen accompanying acute and chronic urticaria. Isolated angioedema without urticarial skin lesions is infrequent and very rare in infants. Angioedema is often idiopathic, but may represent a hypersensitivity reaction to different agents or a manifestation of hereditary angioedema. This autosomal dominant disorder is due to lack (type I) or dysfunction (type II) of C1-inhibitor. There is a third hereditary form with

normal C1 inhibitor levels. In hereditary angioedema, there are recurrent episodes of painful and persistent (24–72 h) swellings on the face and extremities. Gastrointestinal and respiratory tract involvement may occur with severe abdominal pain and life-threatening upper airway obstruction. Onset is usually during late childhood or adolescence. There are rare reports of initial episodes of angioedema in the perinatal period.¹⁷⁹

Diagnosis of isolated angioedema should prompt obtaining C4 levels (the natural substrate for C1 esterase) and C1 inhibitors (antigenic and functional levels).

Autoinflammatory syndromes

Autoinflammatory syndromes refer to a group of diseases in which recurrent systemic inflammation is triggered, often by minor infections, cold temperature, or other innocuous stimuli. Unlike autoimmune diseases, affected patients do not make antigen-specific autoantibodies.¹⁸⁰ Many of these are genetic disorders due to mutations in genes that alter the innate immune system (Box 20.3).^{181,182} Several present in the neonatal period or infancy with prominent skin findings.

CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS)

Three allelic diseases: familial cold urticaria (also called familial cold autoinflammatory syndrome, FCAS); Muckle–Wells syndrome, and chronic infantile neurological cutaneous and articular syndrome (CINCA) (also known as neonatal-onset multisystem inflammatory disease (NOMID)) are now grouped under the umbrella term 'cryopyrin-associated periodic syndromes' (CAPS). They are the result of activating mutations in the *CIAS1* gene, which codifies a protein called NALP3, NLRP3, or cryopyrin. This protein is a key component in the NALP3 inflammasome. Its constitutive activation leads to continuous caspase activation, which leads to an increased conversion of pro-IL-1 β into IL-1 β , resulting in multisystem disease.

BOX 20.3 SELECTED AUTOINFLAMMATORY SYNDROMES WITH SKIN MANIFESTATIONS

HEREDITARY RECURRENT FEVERS

- Cryopyrin-associated periodic syndromes (CAPS)
- Hyper IgD syndrome (HIDS or MK deficiency)
- Familial Mediterranean fever (FMF)
- TNF- α receptor associated periodic syndrome (TRAPS)
- NLRP12-associated periodic fever (NAPS)

PYOGENIC DISORDERS

- Pyogenic arthritis, pyoderma, acne (PAPA)
- Majeed syndrome
- Deficiency of IL-1 antagonist receptor (DIRA) and IL-36 receptor antagonist (DITRA)

GRANULOMATOUS DISEASES

- Blau syndrome

PROTEASOME INSTABILITY DISORDERS

- Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)
- Joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced childhood-onset lipodystrophy (JMP)
- Nakajo–Nishimura syndrome

FAMILIAL COLD URTICARIA

Familial cold urticaria (FCU) is an autosomal dominant disorder characterized by the development of burning wheals, and frequently pain and swelling of joints, stiffness, chills, and even fever after exposure to cold, especially in combination with damp and windy weather.^{183–186} The skin lesions appear on exposed areas and generalize afterwards. Leukocytosis may be present during the attacks. The reaction may be delayed for up to 6 hours after cold challenge. In contrast to acquired cold urticaria, the reaction cannot be elicited by an icecube test; rather, the patient must be subjected to cold environmental temperatures or cold water immersion. On skin biopsy, a neutrophilic infiltrate predominates. The symptoms tend to improve with age. Responses to H₁ and H₂ blockers and ketotifen are poor. Stanazolol has been of limited benefit.¹⁸⁷ FCU has also been described along with amyloidosis and deafness as Muckle–Wells syndrome (MWS).¹⁸⁸ It has been recently demonstrated that both FCU and MWS are due to mutations in the *CIAS1* (cryopyrin) gene; in fact they are the same disorder and may share exactly the same genetic mutation.¹⁸⁹ FCU and MWS are also allelic diseases with CINCA syndrome (see below), which is also due to *CIAS1* gene mutations.¹⁹⁰

CHRONIC INFANTILE NEUROLOGICAL CUTANEOUS AND ARTICULAR SYNDROME (CINCA)

CINCA syndrome,^{191–194} also known as neonatal onset multisystemic inflammatory disease (NOMID), is a chronic systemic inflammatory disease of neonatal onset characterized by skin rash, arthropathy, and CNS manifestations. Cutaneous findings are the presenting signs. The disease follows a chronic course with acute febrile exacerbations, lymph node enlargement, and hepatosplenomegaly. Two-thirds of patients are born prematurely.

Cutaneous findings

A skin eruption is usually the first manifestation of the disease and is present at birth or develops during the first 6 months of life. It is characterized by generalized, evanescent, urticarial macules and papules that migrate over the course of a single day and wax and wane in intensity (Fig. 20.17). The rash is



Figure 20.17 Chronic infantile neurological cutaneous and articular syndrome (CINCA).

typically always present but can worsen with increased disease activity flare-ups. The lesions are usually asymptomatic, but can be pruritic, especially after sun exposure.^{193,194} Geographic tongue and oral ulcers have been noted in a single patient.¹⁹⁴

Extracutaneous findings

Symmetric or asymmetric arthropathy is another constant finding and is severe in half of patients. It is often absent in the first few weeks of life, but usually develops during the first year.^{193,195} The knees are most frequently affected, followed by the ankles and feet, elbows, wrists, and hands. Neurologic signs and symptoms such as headache, vomiting, and seizures develop at a variable age, and intellectual impairment, spasticity, and hypotonia have been described. Progressive sensorineural hearing loss and hoarseness are also common. Ocular disease, an inconstant finding, may include papilledema, uveitis, keratitis, conjunctivitis, and chorioretinitis. Affected children may have a characteristic phenotype with growth retardation, and an increased head circumference, with frontal bossing. Icterus may be present in the neonatal period, especially in patients with severe arthropathy.¹⁹³

Etiology and pathogenesis

Mutations in the *CIAS1* gene have been identified in 60% of patients with CINCA syndrome.^{196,197} In a subset of patients in whom the mutation was not detected by standard techniques, molecular cloning has revealed somatic *CIAS1* mutations.¹⁹⁸ *CIAS1* encodes a protein called ‘cryopyrin’, which is involved in the regulation of apoptosis and the inflammatory signaling pathway.¹⁹⁷ It is proposed that familial cold urticaria and CINCA represent extreme groups of the same disease, defined by the magnitude of phenotypic expression.¹⁹⁷ Considerable clinical overlapping exists between these disorders.

Laboratory tests, radiologic findings, and histopathology

Nonspecific findings typical of a chronic inflammatory process include microcytic anemia; leukocytosis with high neutrophil and eosinophil counts; elevated platelet counts; sedimentation rates, and acute-phase reactants; and polyclonal hyperglobulinemia G, A, or M. Rheumatoid factor and antinuclear antibodies are usually absent. Liver enzymes may be mildly elevated. CSF examination shows pleocytosis and high protein levels.

Radiologic studies of the affected joints show irregularly enlarged, bizarre, spiculated epiphyses with a grossly coarsened trabecular appearance.^{193,195} There is periosteal new bone formation, and growth cartilage abnormalities are frequent. With time, there is bowing deformity of long bones and shortening of diaphyseal length. CT scans of the head have demonstrated hydrocephalus and cerebral atrophy.

Histopathologic examination of the skin reveals interstitial and perivascular neutrophilia.^{194,195} Neutrophilic eccrine hidradenitis has been described.¹⁹⁴ Biopsies of lymph nodes, liver, and synovium show nonspecific signs of chronic inflammation.

Differential diagnosis

CINCA must be differentiated from systemic onset juvenile arthritis. The main differences are its neonatal onset, persistent rash, the short duration of bouts of fever, absence of morning stiffness, and central nervous system involvement. The arthropathy is more deforming, and the radiographic findings of enlarged and disorganized epiphyses are distinctive. In addition,

the response to NSAIDs is poor. Urticaria should also be considered and the predominance of eosinophils in skin biopsy may be a relative clue.

Course, management, treatment, and prognosis

Untreated, the disease follows a chronic course with acute febrile exacerbations and can have a fatal course. Occasionally, it causes death in the first or second decade. Nonsteroidal anti-inflammatory drugs may be effective for pain relief but do not alter the course of the disease. Prednisone has been palliative in doses ranging from 0.5 to 2.0 mg/kg per day.¹⁹⁵ Chlorambucil and penicillamine have been tried, with limited success.^{199,200} Thalidomide has shown beneficial effects in a single patient.²⁰¹ Other choices include methotrexate, the recombinant human IL-1 receptor antagonist anakinra,^{202–205} and the anti-TNF- α agent etanercept.²⁰⁶ Other IL-blocking agents such as rilonacept and canakinumab, are very effective and promising agents.²⁰⁷

PUSTULAR AUTOINFLAMMATORY SYNDROMES IN NEWBORNS

Two syndromes, called deficiency of the IL-1 receptor antagonist (DIRA) and deficiency of the IL-36 receptor antagonist (DITRA), can present in the neonatal period in the form of a severe pustular eruption (see [Chapters 10 and 16](#)).

In DIRA,²⁰⁸ homozygous mutations in the gene *IL1RN* lead to complete absence of the IL-1 receptor antagonist, which leads to an imbalanced IL-1 action causing continuous inflammation with neonatal onset. The eruption appears as crops of pustules or generalized severe pustulosis; histopathology shows extensive neutrophilic infiltration of the dermis and the epidermis. In some cases, DIRA closely resembles pustular psoriasis.²⁰⁹ The skin eruption is accompanied by malaise, but not high-grade fevers. Typically, pain and joint swellings, with epiphyseal ballooning, resembling CINCA syndrome, develop very early in life. Treatment with anakinra (the recombinant IL-1 receptor antagonist) is rapidly effective. If untreated, patients will develop multiorgan failure and may suffer a fatal outcome.

In some families with autosomal recessive pustular psoriasis, appearing as early as one week of life, homozygous missense mutations in the *IL36RN* gene, which codifies the IL-36 receptor antagonist, have been reported.²¹⁰ This disease has been named 'DITRA'. Patients show a diffuse skin eruption with erythema and pustules and high-grade fever. Unlike DIRA, patients with DITRA seldom have other organs involved except the skin, and the skin flares are associated with high-grade fever. It is possible that deficiencies in the IL-36 receptor antagonist are responsible for cases of classic pustular psoriasis.

IMMUNOPROTEASOME-RELATED SYNDROMES

CANDLE syndrome, an acronym for chronic, atypical, neutrophilic dermatosis with lipodystrophy and elevated temperature,²¹¹ describes a group of diseases due to homozygous or compound heterozygous mutations in genes encoding components of the immunoproteasome, mainly the *PSMB8* gene encoding the $\beta 5i$ subunit of the immunoproteasome.²¹² The proteasome and the immunoproteasome are cell structures involved in peptide and protein destruction and/or processing for presentation to the immune system. Ubiquitinated proteins fated to destruction should be recognized by the proteasome/immunoproteasome and cleaved into

smaller peptides. In the absence of a normal proteasome/immunoproteasome function, these proteins accumulate in the macrophages, thus leading to cellular stress; in turn, cellular stress causes activation of the JAK pathway and accumulation of proteins that cannot be destroyed by malfunctioning proteasomes/immunoproteasomes, thus leading to further cellular stress. The end-point in this circle is the release of proinflammatory molecules with a strong interferon signature that leads to the symptoms of the disease.

CANDLE syndrome begins in the first weeks of life in the form of recurrent attacks of erythematous and purpuric plaques and nodules that disappear leaving purpuric residua. They are accompanied by fever. Later in life, the nodules continue to appear, as well as a typical perioral and periocular violaceous swelling. Virtually any organ can be the target of an acute attack of inflammation, which can be fatal. In childhood, a typical lipodystrophy with short stature leads to an unmistakable phenotype. On histopathology, an interstitial infiltrate composed of bizarre mononuclear cells, neutrophils, and leukocytoclasia occupies the dermis and extends into the subcutis.

Two other diseases, called 'JMP syndrome' (an acronym for joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy) and 'Nakajo–Nishimura syndrome' in Japan, are allelic with CANDLE syndrome, and have overlapping manifestations.

There is currently no effective therapy for CANDLE syndrome. NSAIDs, oral corticosteroids and methotrexate can help to control inflammation. No biologic agents, including etanercept, anakinra or canakinumab, have thus far been efficacious.

Eosinophilic cellulitis

Eosinophilic cellulitis or Wells syndrome is a recurrent inflammatory condition, most commonly seen in adults, but cases in infants, and even in newborns^{213–216} have been reported. The pathogenesis of Wells syndrome is not clearly understood. It may represent a hypersensitivity reaction triggered by insect bites, viral and parasitic infections, thimerosal-containing vaccines, or drugs.^{213,217–221} However, in approximately one-half of reported pediatric cases, there was no identifiable precipitating factor.²²² Patients present with persistent erythematous edematous plaques that resolve spontaneously after 2–8 weeks, leaving residual skin hyperpigmentation ([Fig. 20.18](#)). The lesions may



Figure 20.18 Eosinophilic cellulitis. Erythematous edematous plaques with residual crust secondary to blistering.

occasionally become bullous.^{213,223–225} Occasionally, systemic manifestations, including fever, lymphadenopathy, and arthralgias can occur. Recurrences are common, with exacerbations and remissions spanning several years. Peripheral eosinophilia is found in up to 50% of cases in an active phase. Biopsy shows diffuse infiltration of eosinophils within the dermis along with characteristic flame figures caused by the deposition of eosinophil major cationic protein. Older lesions may show a granulomatous histiocytic palisade surrounding the flame figures.²²⁶ The main differential diagnosis is bacterial cellulitis, which is usually tender, warm, lacks pruritus and responds well to antibiotic therapy. Other much less common differential diagnoses include Churg–Strauss syndrome, eosinophilic fasciitis, eosinophilic folliculitis, and hypereosinophilic syndrome.^{227–229}

Wells syndrome is often self-limited. If a treatable precipitating factor can be identified, improvement with treatment of the underlying condition may occur.²²¹ When needed, treatment with topical and systemic corticosteroid therapy alone or in combination has proved useful.²¹³ In recalcitrant cases, dapsone and antihistamines are treatment options.^{213,223} Although Wells syndrome is a benign condition, if the child presents with systemic symptoms or a chronic course, defined as >6 months of peripheral eosinophilia or recurrences of clinical disease, referral to hematology/oncology should be considered.²¹³

Eosinophilic annular erythema of infancy is considered by some authors as a variant of Wells syndrome.^{230,231} Although more common in adults, it has also been reported in infants.^{7,8,232,233} It is characterized by persistent annular lesions, a chronic course, resistance to treatment and high relapse rate. Histopathology shows a perivascular infiltration of eosinophils but without flame figures or granulomas.

Sweet syndrome

Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is a benign disease characterized by tender, raised erythematous plaques, fever, peripheral leukocytosis, histologic findings of a dense dermal infiltrate of polymorphonuclear leukocytes, and a rapid response to systemic corticosteroids.^{234–238} Only a few pediatric cases have been reported,^{239–253} the youngest being 5 weeks of age.²⁴² Two brothers with Sweet syndrome starting at 2 weeks of life have been reported.²⁵⁰

Cutaneous findings

The lesions of Sweet syndrome typically have an acute, explosive onset and are characterized by indurated, tender, erythematous plaques, or nodules that vary in size from 0.5 to 4 cm (Fig. 20.19). Pustules may also be present, though usually at a later stage. The borders may be raised, mammillated, or even vesicular. Some lesions may show central clearing, forming annular or gyrate plaques (Fig. 20.20). The lesions are usually multiple and distributed over the face and extremities or, more rarely, the trunk. Pathergy is not uncommon.²⁵³ Without treatment, they tend to heal spontaneously within a few months. In some patients, especially children, the lesions heal with areas of secondary cutis laxa, also known as ‘Marshall syndrome’.^{241,251,254}

Extracutaneous findings

A high, spiking fever is characteristic but may be absent in up to 50% of patients.²³⁸ Arthralgias or asymmetric arthritis may be associated, and conjunctivitis or iridocyclitis may be seen in one-third of patients.²³⁸ Renal involvement manifesting as



Figure 20.19 Nodular lesions of Sweet syndrome with central crusting.



Figure 20.20 Progression of lesions of Sweet syndrome in the same patient as in Figure 20.19. Plaques and nodules have flattened and are clearing centrally.

proteinuria or hematuria, as well as lung involvement with infiltrates visible on chest radiographs, has also been described. Central nervous system involvement may occur in rare instances and manifests as headaches, convulsions, or disturbance of consciousness. Cerebrospinal fluid pleocytosis with lymphocyte predominance is usually found in such cases.²⁵⁵ Neonatal lupus erythematosus has been reported to present with a neutrophilic dermatosis in newborns.²⁵⁶

Etiology and pathogenesis

The pathogenesis is unknown. Many of the patients reported have had a preceding respiratory tract infection or elevated anti-streptolysin O titers.²³⁸ Of the cases, 10% have been seen in the setting of a variety of hematologic malignancies, particularly acute myeloid and myelomonocytic leukemias.²⁵⁷ Sweet

syndrome has also been associated with solid tumors, inflammatory bowel disease, connective tissue diseases, and chronic granulomatous disease, or it may occur as an adverse reaction to drugs,^{258–260} particularly granulocyte colony-stimulating factor²⁶¹ or after vaccination.²⁶² Because of these associations and the rapid response to systemic corticosteroids, Sweet syndrome is thought to represent a hypersensitivity reaction to infectious agents or tumoral antigens.

Laboratory tests and histopathology

An elevated erythrocyte sedimentation rate and peripheral leukocytosis are frequent accompanying abnormalities. Eosinophilia, microcytic anemia, mild elevation of liver enzymes, and urinalysis abnormalities may be present occasionally. Antineutrophil cytoplasmic antibodies have been detected in some cases.²³⁸ α_1 -Antitrypsin deficiency has been documented in one case of Marshall syndrome.²⁵⁴

The histopathologic findings are diagnostic.²³⁵ There is a dense perivascular infiltrate composed almost entirely of neutrophils. The dermis appears edematous, and subepidermal blisters may form. Spongiosis, exocytosis, and intraepidermal vesiculation may be seen. There is endothelial swelling and nuclear dust, but true vasculitis is characteristically absent.

Differential diagnosis

The lesions of Sweet syndrome may initially resemble those of EM or acute hemorrhagic edema. Lesions on the lower extremities may resemble those of erythema nodosum, but lesions more characteristic of Sweet syndrome are usually present in other locations.

Course, management, treatment, and prognosis

Sweet syndrome itself is a benign disease but may be a marker of malignancy. If left untreated, it resolves spontaneously over weeks to months. However, recurrences are common. Marshall syndrome may have a poorer prognosis, with the development of elastolysis in the lungs or cardiovascular involvement.

Oral corticosteroids are the treatment of choice and usually elicit a prompt response.²⁶³ Potassium iodide administration has been successful in a few cases,²⁶⁴ as have colchicine,²⁶⁵ dapsone,²⁶⁶ clofazimine,²⁵¹ and intravenous immunoglobulin.²⁴⁶

There is considerable clinical and histopathologic overlap between Sweet syndrome and pyoderma gangrenosum in infants.

Kawasaki disease

Kawasaki disease is an acute systemic vasculitis involving small and medium-sized muscular arteries, especially the coronary arteries, of young children.^{267–269} In the past, many cases in very young infants were diagnosed as ‘infantile polyarteritis nodosa’.

Kawasaki disease occurs predominantly in children under 5 years with the peak incidence between 9 and 11 months.^{270–272} It is infrequent before 6 months of age, but has been reported in younger infants, including neonates.^{273–275} Boys are affected 1.5 times as often as girls. Kawasaki disease is an endemic disease with epidemic and geographic clustering. There is seasonal predominance in late winter and spring, although this may differ in different countries.²⁷⁶ Familial cases in household contacts have been described.²⁷⁷ The recurrence rate is 3%, with some patients having two or more recurrences.

Cutaneous findings

The skin is involved in virtually all patients. The initial signs are often diffuse erythema and painful induration of the hands and feet.^{267,278,279}

A polymorphous exanthem on the trunk and proximal extremities usually appears within 5 days of onset of fever (Fig. 20.21). The morphology is most often a nonspecific, diffuse maculopapular or morbilliform eruption, but may be urticarial, scarlatiniform, targetoid, or even pustular. Bullous or vesicular eruptions have not been described. The rash involves the perineum in up to two-thirds of cases, with early desquamation, far earlier than that appearing on the fingers and toes (Fig. 20.22).²⁸⁰

Changes in the lips and oral mucosa include erythema, swelling and fissuring of the lips, strawberry tongue, and erythema of the oropharynx. Oral ulcerations and pharyngeal exudates are not seen. Intermittent acrocyanosis as well as peripheral gangrene have been observed in infants younger than 6 months of age.^{272,281} Inflammatory changes with necrosis at the site of a previous BCG inoculation have also been described.²⁸²

Between 1 and 3 weeks after disease onset, the eruption characteristically begins to desquamate beneath the distal nail



Figure 20.21 (A) Morbilliform eruption in an infant with Kawasaki disease. (B) Cracked lips and early desquamation in the anogenital area in a febrile toddler with Kawasaki disease.

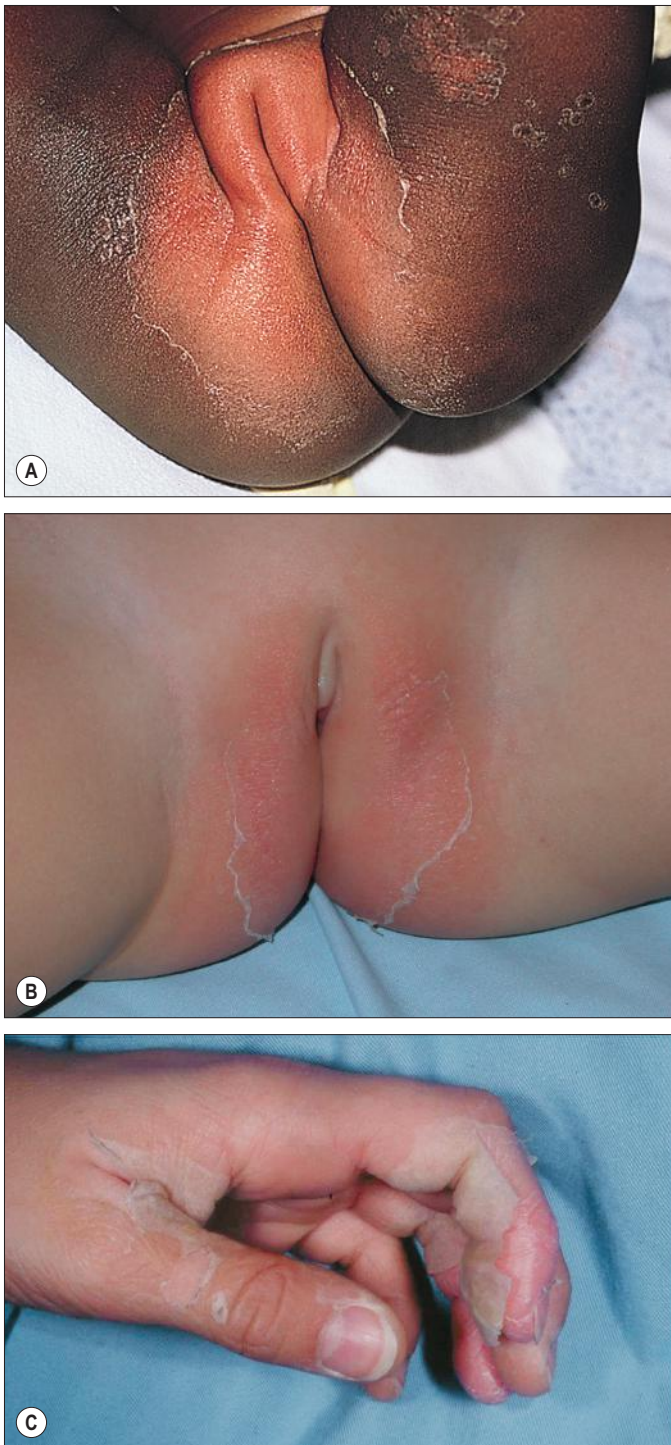


Figure 20.22 (A) Early perineal desquamative eruption of Kawasaki disease. (B) Genital desquamation. (C) Fingertip and hand desquamation in Kawasaki disease.

plates, and peeling may extend to involve the entire palm and sole. Horizontal depressions in the nail plates (Beau's lines) usually result. A maculopapular eruption may appear in the convalescent phase, that may represent an adverse effect of intravenous γ -globulin (IVIG) therapy, as it appears approximately 10 days after the infusion. It is usually self-limited and does not require specific treatment.²⁸³ Plaque-type, guttate, and

pustular psoriasis have been described, either during the acute or the convalescent phase of the disease, which supports a superantigen-mediated etiology.^{284–287}

Extracutaneous findings

Fever lasting for at least 5 days is the cardinal and initial feature of the disease.^{278,279,288,289} It usually begins abruptly and reaches temperatures as high as 39–40°C. Irritability is usually prominent. Other extracutaneous features include nonexudative conjunctival injection, involving mainly the bulbar conjunctivae, anterior uveitis, and cervical lymphadenopathy, which is present in approximately 65% of cases. Enlarged nodes are usually firm, nonfluctuant, slightly tender, unilateral, and confined to the anterior cervical triangle. Cardiac disease is the main cause of long-term morbidity and mortality. The pericardium, myocardium, endocardium, and coronary arteries may all be involved. Without treatment, coronary artery aneurysms develop in 20% of cases, and are most commonly detected 10 days to 4 weeks after onset. Risk factors for the development of coronary aneurysms include age younger than 1 year, male gender, fever for more than 2 weeks, recurrent fever, and delayed treatment. Aneurysms may also develop in systemic medium-sized arteries and result in peripheral gangrene.²⁸¹

Polyarticular arthritis and arthralgias may occur in the first weeks of the illness, affecting small as well as large joints. Lethargy and other signs of aseptic meningitis may be present. Abdominal symptoms such as vomiting, diarrhea, and pain are common. Respiratory symptoms due to pulmonary nodules, infiltrates, or pleural effusion may also be observed.^{290–292} Rare findings include testicular swelling, hemophagocytic syndrome,²⁹³ transient unilateral peripheral facial nerve palsy, and transient high-frequency sensorineural hearing loss (20–35 dB).²⁹⁴

Etiology and pathogenesis

Epidemiologic and clinical data^{295,296} suggest that Kawasaki disease has features of infectious disease in an immunologically susceptible host and of an immune-mediated vasculitis. Many infectious etiologic agents have been suggested as a trigger but none has been consistently demonstrated.²⁹⁵ Regardless of the cause, evidence points to a generalized immune activation with production of various proinflammatory cytokines and endothelial cell activation which lead to coronary artery alteration.²⁶⁸

Host genetic determinants play a role in both susceptibility and coronary artery outcome in Kawasaki disease.²⁹⁷ The incidence rate in siblings is 10 times the population incidence.^{277,298,299} The risk of occurrence in twins is higher than in ordinary siblings. Parents who had Kawasaki disease in childhood are more likely to have affected children, and children with recurrent disease.³⁰⁰

Laboratory tests and histopathology

In the acute phase, laboratory studies show leukocytosis ($\sim 15,000/\text{mm}^3$) with a left shift, normochromic normocytic anemia, increased sedimentation rate and C-reactive protein, depressed albumin, and elevated IgM and IgE levels. After IVIG treatment, the value of ESR becomes uninterpretable due to increased plasma viscosity.²⁷⁹ In the subacute stage, in the second and third weeks of illness, there is a marked and almost universal thrombocytosis, which returns to normal in 4–8 weeks. Thrombocytopenia is rarely seen in the acute stage and

may be a sign of disseminated intravascular coagulation. Plasma lipids are altered in the acute stage, with depressed plasma cholesterol and HDL.³⁰¹ There may be mild elevation of transaminases and polyclonal hypergammaglobulinemia. There may be sterile pyuria with mild proteinuria. Cerebrospinal fluid shows a mononuclear pleocytosis with normal protein and glucose levels. Skin biopsy findings are not specific. There is edema in the papillary dermis, with a mild perivascular mononuclear cell infiltrate. Vasculitis of medium and large arteries is observed.

Diagnosis

Kawasaki disease should be suspected^{267,279} in any patient with fever lasting at least 5 days, nonpurulent conjunctivitis, a polymorphous exanthem, erythema, and swelling of the hands and feet, inflammatory changes of the lips and oral cavity, and acute nonpurulent cervical adenopathy.^{278,288,302,303}

While there is no single diagnostic test for Kawasaki disease, widely accepted clinical criteria have been established for diagnosis (Box 20.4). Incomplete KD is more common in young infants than in older children, making accurate diagnosis and timely treatment especially important in these young patients who are at substantial risk of developing coronary abnormalities. In 2004, the American Heart Association recommended incorporating laboratory tests and early echocardiography for diagnosing incomplete KD. Patients with fever for \geq five days (with 2 or 3 principal clinical features for KD) and infants \leq 6 months old with fever for \geq 7 days without other explanation, should undergo laboratory testing, and if there is evidence of systemic inflammation, an echocardiogram should be obtained even if the patient does not fully meet the clinical criteria for KD (Box 20.4).^{279,290,304} Although aneurysms rarely form before day 10 of illness, there may be signs of coronary arteritis, decreased contractibility, mitral regurgitation, and pericardial effusion. With all these considerations, a new algorithm has been proposed to help in deciding which patient with incomplete Kawasaki disease should undergo echocardiography or receive IVIG treatment (Fig. 20.23).²⁷⁹

Sometimes KD may be 'atypical,' presenting at onset with clinical features that are not generally seen, such as acute abdominal pain, renal impairment, meningeal irritation, pneumonia, or retropharyngeal abscess.

Differential diagnosis

Many diseases mimic Kawasaki disease, including viral infections – particularly adenovirus infection; streptococcal infection; juvenile rheumatoid arthritis; erythema multiforme; SSSS; toxic shock syndrome; drug hypersensitivity reactions; Rocky Mountain spotted fever; leptospirosis; mercury hypersensitivity reaction (acrodynia); and bacterial cervical adenitis. Low white blood cell count, lymphocytosis, and low platelet count may be useful in suggesting a viral infection instead of Kawasaki disease. Mucosal changes, conjunctivitis, extremity abnormalities and perineal desquamation, elevated C-reactive protein and platelet counts suggest the diagnosis of Kawasaki disease.^{305,306}

Course, management, treatment, and prognosis

The morbidity and mortality of KD depend primarily on coronary artery lesions.^{307–311} Coronary artery aneurysms or ectasias develop in 15–25% of untreated children and may lead to ischemic heart disease or sudden death. With early treatment, the risk is reduced to around 5–12%. Small aneurysms resolve

completely within the first 2 years after disease onset in 30–60% of these patients.³¹² However, coronary aneurysms, especially if giant (>8 mm), may persist and be complicated by thrombotic occlusion or the development of stenosis at the outlet of the aneurysm. Stenotic lesions, as well as early coronary atherosclerosis, may develop gradually over several years, so long-term follow-up is warranted.^{309,310,313,314}

Echocardiography should be performed as soon as the diagnosis is suspected and should be repeated at 2 weeks and at 6–8 weeks after disease onset.^{279,315} Other noninvasive imaging modalities, such as MRI, MRA, and ultrafast CT, as well as cardiac stress testing, are being evaluated in the management of Kawasaki disease.

Treatment in the acute phase of the disease is directed to reducing inflammation in the coronary artery wall and preventing coronary thrombosis, whereas long-term therapy in individuals who develop coronary aneurysms is aimed at preventing myocardial ischemia or infarction. Intravenous γ -globulin (IVIG) combined with high-dose aspirin (80–100 mg/kg divided into four) is the treatment of choice in the acute phase of the disease.²⁸⁹ The duration of high-dose aspirin varies in different centers for up to 48–72 after the child has been afebrile for 14 days of illness. Following this acute phase, low-dose aspirin (3–5 mg/kg) is given as an antiplatelet agent for 6–8 weeks from disease onset.

IVIG has been shown to reduce the incidence of coronary artery aneurysms from 20% to 3–4%.^{316–319} A single dose of 2 mg/kg has been shown to be superior than lower doses for 4 consecutive days.^{316,317} IVIG should be started early, within 10 days of disease onset but not before day 5, because it may be associated with an increased need for IVIG re-treatment.^{320,321} Treatment after day 10 should be considered if there are still signs of ongoing inflammation (elevated ESR or CRP) or persistent fever.³²² Some patients with persistent or recrudescing fever require a second dose.³²³

The usefulness of steroids (prednisolone 2 mg/kg per day) in combination with IVIG in the initial therapy of KD is not well established.^{324–327} Steroids have also been used for IVIG treatment failures, but the benefit of pulse methylprednisolone (30 mg/kg for 1–3 days) over a second course of IVIG has not been demonstrated.^{328,279}

Other treatments for IVIG-nonresponsive KD are controversial.^{279,329,330}

Acute hemorrhagic edema

Acute hemorrhagic edema (AHE), also known as 'cockade purpura' and Finkelstein disease, is an acute, benign leukocytoclastic vasculitis of limited skin involvement occurring in children under 2 years of age.^{331–338} AHE has been considered an infantile variant of Henoch–Schönlein purpura; however, because of clinical and prognostic differences, it is sometimes regarded as a separate entity.

Cutaneous findings

The disease is characterized by the abrupt onset of fever; tender edema of the face, eyelids, ears, scrotum, and acral extremities; and ecchymotic purpura on the face and extremities. The trunk is usually spared. Individual lesions often have a darker center and expand centrifugally, giving them a cockade or target-like configuration. Lesions range in size from 0.5 to 4.0 cm and may become confluent, forming polycyclic, annular plaques (Fig.

BOX 20.4 CLASSIC DIAGNOSTIC CRITERIA FOR KAWASAKI DISEASE^a

Fever of 5 days' duration and at least four of the following:^b

1. Changes in the extremities: erythema of palms, soles; edema of hands, feet; periungual peeling of fingers, toes
2. Polymorphous exanthem
3. Bilateral conjunctival injection without exudation
4. Changes in the lips and oral cavity: fissuring, strawberry tongue, diffuse injection of the oral or pharyngeal mucosa
5. Cervical lymphadenopathy of at least 1.5 cm in diameter
6. Exclusion of other diseases with similar findings

OTHER CLINICAL/LABORATORY FINDINGS IN KAWASAKI DISEASE

- Cardiovascular findings
 - Congestive heart failure, myocarditis, pericarditis, valvular regurgitation
 - Coronary artery abnormalities
 - Aneurysms of medium-sized noncoronary arteries
 - Raynaud's phenomenon
 - Peripheral gangrene
- Musculoskeletal system
 - Arthritis, arthralgia
- Gastrointestinal tract
 - Diarrhea, vomiting, abdominal pain
 - Hepatic dysfunction
 - Hydrops of gallbladder
- Central nervous system
 - Extreme irritability
 - Aseptic meningitis
 - Sensorineural hearing loss
- Genitourinary system
 - Urethritis/meatitis
- Other findings
 - Erythema, induration at BCG inoculation site
 - Anterior uveitis (mild)
 - Desquamating rash in groin

LABORATORY FINDINGS IN ACUTE KAWASAKI DISEASE

- Leukocytosis with neutrophilia and immature forms
- Elevated ESR
- Elevated CRP
- Anemia
- Abnormal plasma lipids
- Hypoalbuminemia
- Hyponatremia
- Thrombocytosis after week 1
- Sterile pyuria
- Elevated serum transaminases
- Elevated serum gamma glutamyl transpeptidase
- Pleocytosis of cerebrospinal fluid
- Leukocytosis in synovial fluid

^aPatients with fever of at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease, when coronary artery abnormalities are detected by 2DE or angiography.

^bPatients with four principal criteria can be diagnosed on day 4 of fever.

(Modified from Newburger JW, Takahashi M, Gerber MA, et al., *Pediatrics* 2004 Dec; 114(6):1708–1733.)

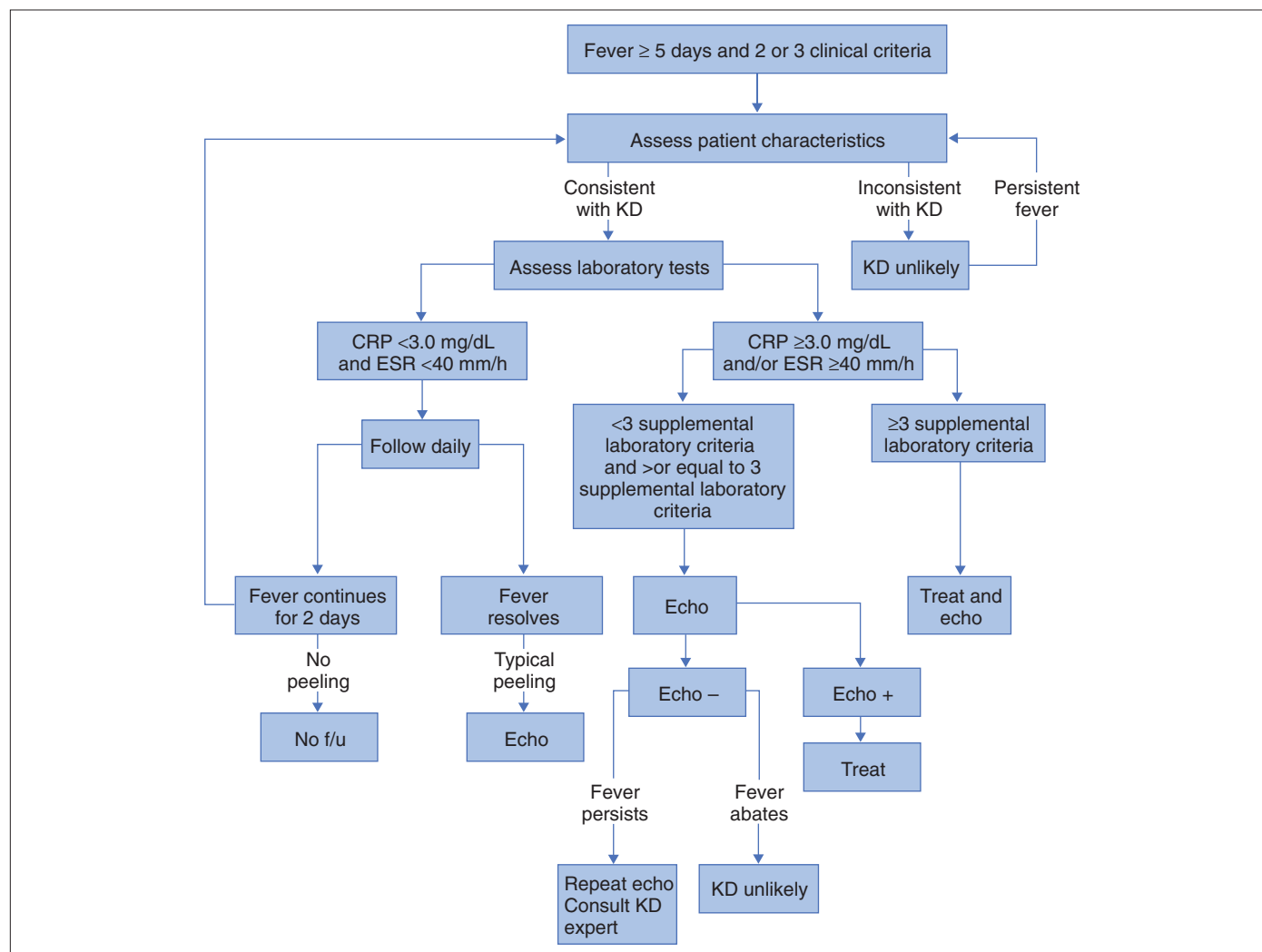


Figure 20.23 Evaluation of suspected incomplete Kawasaki disease. (Modified from Newburger JW, Takahashi M, Gerber MA, et al. *Pediatrics* 2004; 114(6):1708–1733.)

20.24). Necrotic^{337,339} and bullous lesions may be seen,^{337,340} as well as petechiae involving the mucous membranes.³⁴¹

Extracutaneous findings

Except for fever, there are usually no associated manifestations in most cases. Gastrointestinal symptoms, including abdominal pain, diarrhea and intussusception have been reported occasionally.^{338,342,343} In many patients, there is a preceding upper respiratory tract infection. The dramatic cutaneous findings contrast with the general well-being of the patient.

Etiology and pathogenesis

The cause of AHE is unknown. It is thought to represent an immune complex-mediated disease precipitated by a preceding infection, particularly an upper respiratory tract infection, drug intake, or immunization. *Staphylococcus* and *Streptococcus* spp. and viruses (adenoviruses, rotavirus) have been implicated most commonly.^{338,340}

Laboratory tests and histopathology

Leukocytosis (both lymphocytic and granulocytic), thrombocytosis, eosinophilia, and an elevated ESR may be present. Urinalysis, tests for occult blood in the stool, immunoglobulin, and complement levels are usually normal or negative. Circulating immunocomplexes may occasionally be found.³⁴⁰

Histopathologic examination of skin biopsy specimens demonstrates a small vessel leukocytoclastic vasculitis. Direct immunofluorescence shows deposition of C3 and fibrinogen in the vessel wall. IgM, IgG, IgA, and IgE deposition has also been noted in up to one-third of cases.^{340,344–346}

Differential diagnosis

The differential diagnosis includes Henoch–Schönlein purpura, child abuse, meningococcemia and other infectious purpuras, erythema multiforme, Kawasaki disease, and Sweet syndrome.^{331,341} Distinction from Henoch–Schönlein purpura may be difficult (Table 20.5).³³⁸ Perivascular deposits of IgA are not useful for differentiation because they may be present in both entities.

Course, management, and prognosis

The prognosis is excellent. The eruption resolves spontaneously without sequelae in 1–3 weeks. Treatment with corticosteroids

is not necessary and may lead to complications and worsen the prognosis.³⁴⁴ Exacerbations may be observed during the clinical evolution, with new crops of lesions and fever,^{339,345} but true recurrences weeks or months after the first episode are rare.^{338,341} There has been a single report of a fatal ileo-ileal intussusception in an infant with cutaneous lesions otherwise typical for AHE,³³⁹ and recurrent AHE was the presenting manifestation of Wiskott–Aldrich disease in another.³⁴⁷

Henoch–Schönlein purpura

Henoch–Schönlein purpura (HSP) is a systemic small vessel IgA-mediated vasculitis affecting the skin, joints, gastrointestinal tract, kidney and central nervous system. It is the commonest form of vasculitis in childhood. Most cases occur in children of 4–11 years of age, although it has also been reported in infants.^{348,349}

The characteristic clinical picture consists of palpable purpura along with arthralgia, abdominal pain and hematuria. The onset may be acute with simultaneous involvement of multiple organs or more subtle with gradual emergence of different manifestations over a few months. The diagnosis of Henoch–Schönlein purpura is mainly clinical. Proposed diagnostic criteria of the American College of Rheumatology include: (1) palpable purpura; (2) age at onset under 20 years; (3) evidence of intestinal angina or ischemic bowel such as abdominal pain that worsens with meals or bloody diarrhea; (4) evidence of small vessel leukocytoclastic vasculitis. The presence of two of these criteria has a sensitivity of 87.1% and a specificity of 87.7% for the diagnosis of Henoch–Schönlein purpura. These criteria have been widely criticized, as any child with palpable purpura would be diagnosed, even if they had another cause for vasculitis without concomitant risk of renal disease. Others argue that the presence of IgA, either in the cutaneous or renal biopsy, is mandatory to make the diagnosis of HSP.³⁵⁰

Cutaneous findings

Skin lesions are always present, and are the first manifestations in 75% of cases,^{348,349} but in some cases, joint involvement or abdominal pain precedes the rash by up to 2 weeks. Initially,



Figure 20.24 Acute hemorrhagic edema.

TABLE 20.5	Differential diagnosis between acute hemorrhagic edema and Henoch–Schönlein purpura	
	Acute hemorrhagic edema	Henoch–Schönlein purpura
Onset	Acute and dramatic	Less dramatic
Age	2 months–2 years	>2 years
Sex	Male predominance	Male predominance
Location	Face, ears, extremities	Lower extremities, buttocks
Morphology	Large medallion-like purpura Facial edema	Palpable purpura Edema of lower extremities
Course	No recurrences	Frequent relapses
Histopathology	Leukocytoclastic vasculitis	Leukocytoclastic vasculitis
Immunodeposits	Variable IgA, IgM, C3	IgA
Systemic involvement	No	Renal, gastrointestinal, joint, CNS

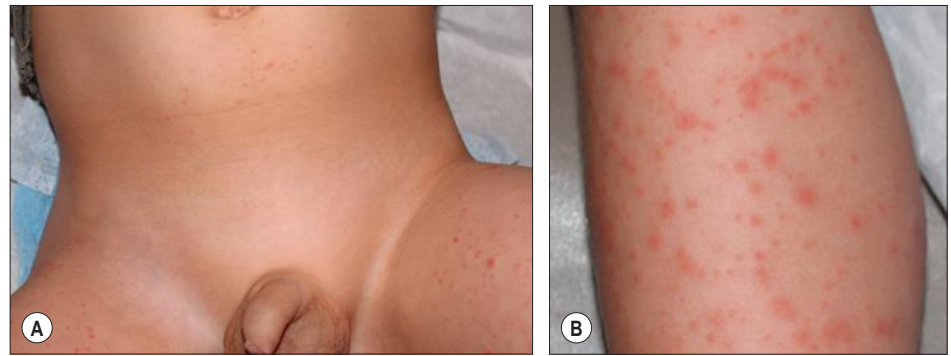


Figure 20.25 Henoch-Schönlein purpura. Purpuric lesions on (A) the thighs and lower abdomen and (B) distal leg.

skin lesions may be urticarial or appear as an erythematous macular-papular rash before evolving to palpable purpura. The purpuric papules are typically 2–5 mm in size, symmetrically distributed on the legs and buttocks (Fig. 20.25). In cases with severe vascular damage, there may be large ecchymoses as well as blistering and necrosis. Lesions may appear at sites of trauma (Koebner phenomenon) and on more atypical locations such as the face, trunk, or arms, but they rarely affect mucosa, palms, and soles. In younger children, there may be painful swelling of the scalp, face, periocular region, ears, limbs, and scrotum, mimicking testicular torsion.³⁴⁸ The lesions heal spontaneously within 1–2 weeks, but exacerbations often occur in the course of the disease.

Extracutaneous findings

Joint involvement is present in 60–80% of cases and is the first manifestation in 25% of cases.^{348,349} Knees and ankles are most often involved, showing a self-limiting non-migratory arthritis. Gastrointestinal involvement is the first manifestation in 15% of cases. Periumbilical pain that worsens with meals and accompanied by bloody diarrhea, is the most characteristic, although bleeding may occur in the form of melena, hematochezia or fecal occult blood, even in the absence of pain. Major but rare complications include intestinal perforation and intussusception,^{349,351} and there are anecdotal reported cases of cholecystitis and pancreatitis.³⁵¹ Renal involvement varies widely from 10% to 60% of cases and it is the latest symptom;³⁴⁹ it usually appears within the first 6 weeks of the start, but can take up to 6 months. The main manifestation of renal involvement is microscopic hematuria with or without proteinuria, that may evolve into nephrotic syndrome, acute nephritis (7% of patients), and acute renal failure (2%). Renal involvement is the main negative prognostic factor, and is more common in children >4 years, with more abdominal pain, decreased activity of factor XIII and persistence of purpura for more than 1 month.^{349,352} Central nervous system involvement is infrequent, with varied manifestations, e.g., headache, irritability, convulsions, and occlusion of the central artery of the retina. Pulmonary involvement is exceptional in children, and commonly manifests as diffuse alveolar hemorrhage.³⁴⁸

Etiology and pathogenesis

The pathogenesis of HSP is not yet clearly understood, although it is known to be an immune complex-mediated disease. Many infectious agents have been reported to trigger HSP, as have several vaccinations. Other triggers are insect bites and certain medications. Multiple factors have been implicated, including human leucocyte antigen class II genes, genetic polymorphisms

of the renin angiotensin system and cytokines such as IL-1 β .^{353,354} HSP is also more common in children with familial Mediterranean fever.³⁵⁵

Laboratory findings and histopathology

Laboratory studies may show anemia, leukocytosis and variably increased ESR. Coagulation studies, ANA, IgM, and IgG are all normal. In some cases, elevated levels of IgA, IgA circulating immune complexes, IgA rheumatoid factor, and IgA antineutrophil cytoplasmic antibodies can be detected.^{349,352} Urinalysis may show hematuria and proteinuria. ASO titers are raised in cases of preceding streptococcal infection. In cases of renal impairment, elevated creatinine, and hypoalbuminemia may be observed. Skin biopsy shows small vessel leukocytoclastic vasculitis. Immunofluorescence studies demonstrate perivascular deposits of IgA, C3 and fibrinogen in recent lesions.

Differential diagnosis

Differential diagnosis should rule out other forms of small vessel vasculitis with similar symptoms such as systemic lupus erythematosus, Wegener disease or cryoglobulinemia. In young children, the main differential diagnosis is acute hemorrhagic edema, as there is some degree of clinical overlap.

Treatment and prognosis

In the absence of renal involvement, treatment of Henoch-Schönlein purpura is only symptomatic. NSAIDs are useful in controlling joint pain. Systemic steroids have been recommended in cases of major abdominal involvement, but they do not seem to prevent renal involvement and their overall role is controversial.^{356,357} Renal disease should be managed by a nephrologist.

Henoch-Schönlein disease is usually self-limiting within 2–4 weeks. Up to one-third of patients have 2–3 recurrences, sometimes months or even 1 year after the first episode. As the renal involvement may appear later in the disease course, monitoring renal functions for at least 6 months after the cutaneous lesions have resolved, is recommended.³⁵⁸

Photosensitivity disorders

The photosensitivity disorders^{359,360} are a heterogeneous group of diseases linked to an abnormal response of the skin to ultraviolet radiation. They should be suspected if the child experiences a sunburn reaction, intense pruritus, unexplainable discomfort or scarring in sun-exposed areas after a limited sun exposure, or when there is family history of photosensitivity disorder. The rash usually involves the face, neck and

TABLE
20.6

Photosensitivity disorders

Immunologically mediated	Secondary to exogenous agents	Photoaggravated disorders	Hereditary photodermatoses
Polymorphous light eruption Solar urticaria Hydroa vacciniforme Actinic prurigo	Photoallergic contact dermatitis Phototoxic contact dermatitis Photosensitivity to systemic agents	Atopic dermatitis Seborrheic dermatitis Bullous pemphigoid Lupus erythematosus Juvenile dermatomyositis Erythema multiforme Pellagra Viral infections Psoriasis Infantile acne Darier disease	Porphyrias Xeroderma pigmentosum Rothmund–Thomson syndrome Bloom syndrome Cockayne syndrome Ultraviolet-sensitive syndrome Kindler syndrome Trichothiodystrophy Smith–Lemli–Opitz syndrome Hartnup syndrome

sun-exposed areas of the limbs such as dorsum of hands and feet, but spares the retroauricular area, upper lip, and submental region, as these are areas naturally protected by the ears, nose, and chin. Photosensitivity disorders can be categorized into four groups (Table 20.6). To reach the diagnosis a thorough past medical history and physical exam are essential, and, as appropriate, laboratory assessments, a skin biopsy and genetic testing. Phototesting may also be useful in selected conditions. Prompt recognition of photosensitivity permits early diagnosis and prevention of later complications.

IMMUNOLOGICALLY MEDIATED PHOTOSENSITIVITY DISORDERS

This group of disorders is of unknown etiology, although immunological disturbances are most probably involved. Polymorphous light eruption is the most common idiopathic photosensitivity disorder, but it is rare in children and has not been reported in infants. Similarly, solar urticaria is rare in both adults and children and does not present before 2 years of age, so only *hydroa vacciniforme* and *actinic prurigo* will be discussed.

Hydroa vacciniforme (HV) is a rare photosensitivity disorder that typically appears in childhood. It is characterized by erythematous papules and vesicles that appear a few hours after sun exposure, then become necrotic and resolve leaving atrophic varioliform scarring (Fig. 20.26). The lesions may be preceded by burning and stinging complaints during sun exposure. Eye and oral mucosal involvement have been reported.³⁶¹ Although the etiology is unknown, some studies have found a pathogenic link between HV and Epstein–Barr virus infection.^{362,363} Phototesting is not diagnostic but the lesions can be reproduced both with UVA and UVB radiation.³⁶⁴ Histopathology shows epidermal necrosis, intraepidermal vesicles with spongiosis and a superficial perivascular lymphocytic infiltration. The diagnosis is based on clinical features; however, other photosensitivity disorders such as lupus erythematosus and porphyrias must be ruled out. Photoprotection with clothing and sunscreen is only partially successful in preventing new lesions. Oral B carotene,³⁶⁵ as well as antiviral therapy with aciclovir and valacyclovir³⁶² have proved useful in some patients. Patients usually present with recurrent outbreaks for years that ameliorate with age, but scarring is permanent. Complications of HV are rare. Atypical cases of Epstein–Barr virus-related HV evolving into lymphoma seem to represent a different entity.^{366,367}



Figure 20.26 Hydroa vacciniforme. Vesicles, crusts, and erosions on the nose after sun exposure.

Actinic prurigo (AP) is a photosensitivity disorder that, although rare, is commonly seen in children. Most cases begin in the first decade of life and patients have family history of the disease. The condition is primarily seen in Native Americans and reported less frequently in Caucasian and Asian populations. In Caucasians, it is associated with HLA DR4 (in particular the DRB1*0407 subtype),³⁶⁸ while in the Native American population, especially prone to AP, it has been associated with the A-24 and HLA Cw4.³⁶⁹ It is characterized by seasonal outbreaks, in spring and summer, of itchy papules, plaques and nodules that often leave post-inflammatory scarring (Fig. 20.27). The lesions are mainly located on sun-exposed areas, but may also appear in areas not exposed to sunlight. Cheilitis and conjunctivitis are common,^{370,371} as well as the presence of chronic lichenified plaques in older patients. Neither phototesting nor skin biopsy are specific, and diagnosis should be based on clinical features. AP responds poorly to photoprotection. The administration of carotenoids, high potency

corticosteroids phototherapy (UVB or PUVA) and even thalidomide have proven useful in some cases.^{372–374}

PHOTOSENSITIVITY DISORDERS INDUCED BY EXOGENOUS SUBSTANCES

Photosensitivity reactions induced by exogenous substances occur when ultraviolet light interacts with a systemically delivered or topically applied agent. This group includes photoallergic contact dermatitis, rare in children, photoirritant contact dermatitis, much more common, and photosensitivity secondary to systemic administration of substances, especially medications, which is more common in adults and older children. The main differences between phototoxic and photoallergic reactions are shown in Table 20.7.

Photoallergic contact dermatitis (PACD) is believed to be a cell-mediated delayed hypersensitivity reaction that occurs when ultraviolet light is absorbed by the photoantigen. The individual must first be sensitized to the allergen, which can require 7–10 days, but after the first sensitization, subsequent reactions appear in a few hours after exposure to the sun in the form of urticarial, papular, or eczematoid lesions typically not followed by hyperpigmentation. Sunscreens with chemical components (mainly benzophenones) and topical nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common cause of PACD, but both are rarely used in infants.^{375,376} Octocrylene, another chemical ultraviolet filter now used in sunscreens, has been reported to cause PACD in children less than 3 years of age.³⁷⁷ PACD may be confirmed by photopatch testing, but it may be difficult to perform in this age group. Therapy consists of avoidance of the offending agent and mild topical steroids.

Phototoxic contact dermatitis (PTCD) is caused by an interaction between a topically applied substance and sunlight in the A wavelengths. This can occur in young infants, due to exposure to photosensitizing agents, particularly plants containing psoralens or furanocoumarins, such as lime, parsley, clover, celery, figs, and meadow grass. PTCD reactions to plant psoralens are known as ‘phytophotodermatitis’. Children exposed to colognes containing bergamot oil, from the natural psoralen-containing fragrant fruit, can also develop phytophotodermatitis (sometimes referred to as Berloque dermatitis).³⁷⁸ Acute inflammatory lesions usually develop within 12–36 hours after exposure and typically have a linear or bizarre distribution (Fig. 20.28). Later on, they evolve with prominent post-inflammatory hyperpigmentation that usually last several months.³⁷⁹ A detailed clinical history is essential for diagnosis, as some cases have been misdiagnosed as child abuse, atypical bruising associated with malignancy, burns, and fungal or viral infections.^{380–382} Treatment is based on avoidance of contact with the causative agent and supportive measures.

Photosensitivity to systemic agents must be suspected in children with erythema, papules, or pigment alteration in photo-distributed areas while, or after, the patient is on systemic medication. Although there are many drugs that may cause phototoxic reactions, most of them are not used in infants. Voriconazole-related phototoxicity has been reported in a 1-month-old baby,³⁸³ as well as methylene-blue and fluorescein-induced phototoxicity after phototherapy in neonates.^{384,385}

PHOTOAGGRAVATED DERMATOSES

Some dermatoses not directly caused by sunlight exposure may occasionally be aggravated by it. Table 20.6 lists the

Figure 20.27 Actinic prurigo. (A) Erythematous, edematous and vesicular plaques on the cheek, nose and chin and (B) papules and crusts on the forearms and dorsal surfaces of the hands.



TABLE 20.7

Main differences between phototoxic and photoallergic reactions

Clinical manifestations	Phototoxic	Photoallergic
Occurrence after first exposure	Yes	No (requires prior sensitization)
Onset of eruption after exposure	Minutes to hours	24–48 hours
Clinical findings	Sunburn-like reaction/hyperpigmentation	Varied morphology, usually eczematous
Distribution	Exposed skin only	Exposed skin but may spread to unexposed areas
Common topical culprit agents	Plants (phytophotodermatitis)	Sunscreens with benzophenones or octocrylene

photoaggravated dermatoses most frequently seen in young children. The ultraviolet-exacerbated eruption is usually limited to the areas involved by the underlying condition, but may also involve other sun-exposed areas.

GENODERMATOSES WITH PHOTSENSITIVITY

A number of inherited disorders may manifest with photosensitivity. We have divided this group into porphyrias and hereditary photodermatoses resulting from defects in DNA repair or metabolic abnormalities other than the heme biosynthesis pathway (Table 20.8). Specific extracutaneous manifestations as well as laboratory and genetic testing will help to make the definite diagnosis.



Figure 20.28 Phototoxic reaction to lime.

The porphyrias

The porphyrias^{386–394} are a group of diseases characterized by abnormalities of porphyrin–heme metabolism. Each type results from deficient activity of one of the enzymes of the heme biosynthetic pathway, which leads to an accumulation of heme precursors within plasma, red blood cells, urine, and feces (Table 20.6).³⁹⁴ The genes for these enzymes have been characterized.^{386,388,394} Porphyrias are mainly inherited in an autosomal dominant manner with incomplete penetrance, but autosomal recessive and more complex patterns of inheritance are present in some forms. Porphyrias are classified as *hepatic* or *erythropoietic*, according to the organ site in which the underlying defect of heme synthesis is predominantly expressed (Table 20.9). They are also classified into cutaneous or acute porphyrias according to clinical manifestations. Cutaneous manifestations in porphyrias may be classified as acute photosensitivity with burning pain, edema, and erythema shortly after sun exposure without blisters, or delayed photosensitivity manifesting as skin fragility, subepidermal blisters, milia, disorders of pigmentation, and sclerodermoid signs. Acute porphyrias are those that present neurovisceral attacks with abdominal pain and neuropsychiatric manifestations.

Hepatic porphyrias usually manifest acute neurovisceral attacks and delayed photosensitivity, and rarely present before puberty except from the homozygous variants. Elevated porphyrins may be detected in the stool or urine.

Erythropoietic porphyrias are characterized by acute cutaneous photosensitivity from early childhood. The more delayed photosensitivity, although less characteristic of this type of porphyria, may be also present.³⁹² Erythrocyte and plasma porphyrin levels are elevated in erythropoietic porphyrias.

Photosensitivity in porphyrias is maximum for ultraviolet wavelengths between 400 and 410 nm ('Soret band') within the visible light spectrum, which can be transmitted through window glass, and also in the range of indoor fluorescent light.

TABLE
20.8

Main findings in genetic photosensitivity disorders

Disorder	Pattern of inheritance	Early cutaneous manifestations	Other skin manifestations	Associated findings	Causative gene and function
Xeroderma pigmentosum	AR	Photosensitivity, freckling, photophobia and conjunctivitis	Actinic damage including poikiloderma, actinic keratosis and photoaging Melanoma and non-melanoma skin cancer in childhood	Cognitive impairment, hearing loss, hyporeflexia, spasticity, seizures (types A and G, usually not in XP variant)	XP A-G and XP variant Nucleotide excision repair (NER) abnormality
Cockayne syndrome (CS)	AR	Photosensitivity with pigmentary changes only in cases of combined xeroderma pigmentosum-Cockayne syndrome	Thinning of skin and hair Skin cancer in combined XP-CS cases	Loss of adipose tissue, prominent ears, short stature ('cachectic dwarfism') Microcephaly Dental caries Mental retardation Deafness Pigmentary retinal degeneration Basal ganglion calcification Osteoporosis	ERCC8 (CSA) and ERCC6 (CSB) XPB, XPD and XPG in combined WP-CS phenotypes Nucleotide excision repair (NER) abnormality

TABLE
20.9

Classification of the porphyrias, enzymatic defect, porphyrin profile, and age of onset

Tissue origin	Type	Enzyme deficiency	Porphyrin profile				Age of onset
			Erythrocyte	Plasma	Urine	Stool	
Erythropoietic	Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III synthase	URO-I, COPRO-I, PROTO	URO-I, COPRO-I, PROTO	URO-I > COPRO-I	COPRO-I	Birth, infancy
	Erythropoietic protoporphyria (EPP)	Ferrochelatase	PROTO	PROTO	Normal	PROTO	Infancy, early childhood
Hepatic	Acute intermittent porphyria (AIP)	Porphobilinogen deaminase	Normal	Normal	ALA, PBG	Normal	After puberty, no cutaneous manifestations
	Variegate porphyria (VP)	Protoporphyrinogen oxidase	Normal	COPRO, PROTO	COPRO > URO	PROTO > COPRO	2nd decade, homozygous variant at birth, infancy, or early childhood
	Hereditary coproporphyria (HCP)	Coproporphyrinogen oxidase	Normal	COPRO	COPRO	COPRO	After puberty, homozygous variant (harderoporphyria) at birth, infancy, or early childhood
	Porphyria cutanea tarda (PCT) ALA dehydratase porphyria	Uroporphyrinogen decarboxylase ALA dehydratase	Normal	URO	URO-I > III	ISOCOPRO	3rd or 4th decade
Hepatoerythropoietic	Hepatoerythropoietic porphyria (HEP)	Uroporphyrinogen decarboxylase	Zn-PROTO	ALA, COPRO, PROTO, URO	ALA, COPRO, URO	COPRO, PROTO	Any age, no cutaneous manifestations
				URO	URO-I (I and III)	ISOCOPRO	Early infancy

ALA, 5-aminolevulinic acid; COPRO, coproporphyrin; ISOCOPRO, isocoproporphyrin; PBG, porphobilinogen; PROTO, protoporphyrin; URO, uroporphyrin.

TABLE
20.8

Main findings in genetic photosensitivity disorders (Continued)

Disorder	Pattern of inheritance	Early cutaneous manifestations	Other skin manifestations	Associated findings	Causative gene and function
Trichothiodystrophy	AR	Ichthyosiform erythroderma (w/wo collodion baby) Sparse brittle hair Photosensitivity (42% cases)	Hair shaft abnormalities (tiger tail banding with polarized microscopy) Dry skin, eczema, freckles, onychodystrophy Variable risk of skin cancer	Maternal pregnancy complications Low birthweight Microcephaly, protruding ears, micrognathia Short stature Intellectual impairment Abnormal gait Decreased fertility Infantile or congenital cataracts Recurrent infections No mental retardation	<i>XPB</i> , <i>XPB</i> , <i>TTDN1</i> Nucleotide excision repair (NER) abnormality (<i>XPB</i> and <i>XPB</i>) and unknown function (<i>TTDN1</i>)
UV-sensitive syndrome	AR	Mild variant of CS	Mild variant of CS No higher risk of skin cancer		<i>UVSSA</i> gene Defective transcription-coupled repair (<i>TC-NER</i>)
Rothmund–Thomson syndrome	AR	Erythema, edema and blistering on cheeks, buttocks and limbs	Poikiloderma on sun-exposed and non-sun-exposed areas Sparse hair, eyebrows and eyelids Abnormal nails Skin cancer (adulthood)	Short stature Skeletal abnormalities Juvenile cataracts Dental abnormalities Hypo-gonadism Osteosarcoma Normal intelligence	<i>RECQL4</i> DNA helicase abnormality
Bloom syndrome	AR	Malar erythema and telangiectasias Pigmentary changes Skin atrophy	Café-au-lait macules Hypopigmented areas Acanthosis nigricans Epithelial skin cancer rarely	Elongated facies, prominent nose, malar hypoplasia, short stature High-pitched voice Decreased IgA, IgM, variable IgG Recurrent GI and lung infections Increased risk of hematological and GI malignancies Diabetes mellitus Normal intelligence and sexual development but reduced fertility	<i>RECQL3</i> DNA helicase abnormality
Kindler syndrome	AR	Blistering Photosensitivity	Skin atrophy on dorsum of hands Sclerosing features on hands and feet Webbing Pseudoainhum Poikiloderma Epithelial skin cancer (adulthood)	Mucosal fibrosis involving oral, ocular, gastrointestinal, anal, and genitourinary affection.	<i>FERMT1</i> Focal adhesion protein involved in architecture, polarization and boundary to the dermis of keratinocytes
Smith–Lemli–Opitz Syndrome	AR	Photosensitivity (57%)	No pigmentary changes No skin cancer	Hypospadias Microcephaly and facial dysmorphism Mental retardation Congenital heart defects Short thumbs Syndactyly of 2nd and 3rd toes	<i>DHCR7</i> (7-dehydrocholesterol reductase) involved in cholesterol biosynthetic pathway
Hartnup syndrome	AR	Photodistributed pellagra-like scaly erythematous plaques Cheilitis	Acrodermatitis enteropathica-like lesions No skin cancer	Cerebellar ataxia, seizures, neurological impairment Diarrhea	<i>SLC6A19</i> Epithelial tryptophan-transporter protein

The pathophysiologic mechanisms involved in the cutaneous manifestations of the porphyrias are multiple and involve the creation of reactive oxygen species.^{395–397}

Childhood porphyrias are relatively uncommon and their exact incidence is unknown. Only those porphyrias manifesting early in infancy are reviewed here.

CONGENITAL ERYTHROPOIETIC PORPHYRIA

Congenital erythropoietic porphyria (CEP), also called Günther disease, is a rare autosomal recessive disorder caused by deficient activity of uroporphyrinogen III (UROGEN III) synthase. Elevated levels of URO-I and COPRO-I in erythrocytes can result in massive hemolysis, and the released porphyrins accumulate in peripheral blood, skin, bone, and teeth and are excreted in large amounts in the urine and feces.

Cutaneous and extracutaneous findings

CEP presents with severe photosensitivity and marked skin fragility from birth or early infancy with formation of vesicles and bullae on areas exposed to sun, phototherapy devices, pulse oximeter sites, or even ambient lighting.^{391,398–401} The severity and age of onset depends on the genotype and residual enzyme activity.⁴⁰² A brownish amniotic fluid or brown-red urine, which can cause pink discoloration of the diapers (fluorescing with Wood's light) can precede these findings. In severe cases, infants are very ill either at birth or in early infancy with a hemolytic anemia, which can even result in hydrops fetalis. Skin fragility can result in severe mutilating scars affecting the fingers, hands, and face, particularly the nose and ears. Hypertrichosis of the face and extremities, scarring alopecia of the scalp and eyebrows, and pigmentary changes (hyperpigmentation and hypopigmentation) are also common.

Ocular changes include ectropion, photophobia, and keratoconjunctivitis.⁴⁰³ Other manifestations include splenomegaly, osteodystrophy with increased bone fragility, and porphyrin-rich gallstones.

Patients with late-onset disease may not develop hemolytic anemia but only thrombocytopenia and myelodysplasia.

Laboratory tests and histopathology

Histologic examination of skin biopsy specimens from blisters reveals subepidermal cleavage (within the lamina lucida) and minimal inflammatory infiltrate. Perivascular accumulation of PAS-positive, diastase-resistant, homogeneous hyaline material (porphyrins) may be seen, which is best viewed with fluorescence microscopy. See Table 20.9 for porphyrin excretion profile. Measurement of URO III synthase activity is available.

Mutational analysis for UROGEN III synthase, localized on chromosome 10, can help confirm diagnosis. Several mutations have been identified,⁴⁰⁴ and different mutations correlate with the level of residual enzyme activity and hence with disease severity and genotypes.^{402,405,406}

Prenatal diagnosis is possible by either measurement of uroporphyrin I from amniotic fluid or via direct gene mutation analysis.^{407–410}

Differential diagnosis

Other photosensitivity diseases presenting early in life or diseases manifesting with blisters, such as epidermolysis bullosa, should be considered. The distribution of blisters in light-exposed areas helps in finding the correct diagnosis. Prenatally,

clues to the diagnosis of CEP include fetal hydrops, fetal ascites, severe anemia, oligohydramnios, and increased maternal serum alpha fetal protein.

Management

Photoprotection is an essential part of management.⁴¹¹ Protective clothing and physical sunblocks are necessary as chemical sunscreens are not protective against Soret band radiation. Long-wavelength, UV-absorbing films are encouraged on car windows and windows at home. Children with the severe phenotypes may benefit from repeated erythrocyte transfusions and hydroxyurea to suppress erythropoiesis and the production of endogenous porphyrins. Hematocrits should be maintained above 32%, with appropriate iron chelation. The efficacy or repeated erythrocyte transfusion may decrease at puberty. Subsequent splenectomy is often needed to control hemolytic anemia.^{412,413} Activated charcoal,^{414–417} and β -carotene^{418,419} have been used, with inconsistent results. Allogeneic bone marrow transplantation can be curative in severe cases but has its own potential risks.^{420–424}

ERYTHROPOIETIC PROTOPORPHYRIA

Erythropoietic protoporphyria (EPP)^{386,397,425} is the most common form of cutaneous porphyria presenting in childhood. EPP is caused by deficient activity of ferrochelatase, leading to the accumulation of protoporphyrin in erythrocytes, plasma, and feces. Clinical symptoms typically begin in infancy or early childhood, with a peak incidence between 2 and 4 years of age. EPP is usually inherited as an autosomal dominant condition. Even those individuals carrying the gene may be asymptomatic, because a reduction of enzymatic activity to below a critical threshold of about 35% of normal is required for clinical expression. Some cases are due to autosomal recessive inheritance.^{426–428}

Clinical manifestations

Most affected patients have an acute phototoxic reaction, with burning pain or stinging sensations on exposed areas (the face and the dorsal aspect of hands). In infants, this often manifests as crying within minutes of sunlight exposure even in the absence of visible skin changes. Erythema, edema, and urticarial lesions are common findings, but vesicles and bullae are rare (Fig. 20.29). Fine petechiae may occur on sun-exposed areas after prolonged exposure. Some patients have only subjective symptoms.⁴²⁵ With chronic exposure, there is characteristic thickening and wrinkling of the knuckle pads, furrowing around the mouth (pseudorhagades), and shallow elliptical scars on the nose, cheeks, and forehead.

Extracutaneous findings are uncommon. Hemolytic anemia is absent, but in some patients, a mild hypochromic, microcytic anemia may occur. Protoporphyrin-rich gallstones may develop in childhood. Fatal liver failure resulting from the progressive accumulation of protoporphyrin in hepatocytes is a possible outcome in about 2.5% of patients, altering the prognosis for an otherwise clinically benign disorder. Recessive inheritance may predispose to severe liver disease.^{426,429}

Diagnosis

The diagnosis is most often established via measurement of free erythrocyte protoporphyrins in the blood in the setting of typical clinical findings. Histopathologic examination of skin



Figure 20.29 Erythrocytic protoporphyria. (Courtesy of Henry Lim and Tor Schwyder.)

biopsy specimens of sun-exposed areas shows marked concentric deposits of PAS-positive diastase-resistant hyaline material around dermal blood vessels.

The gene for ferrochelatase is localized on chromosome 18. Over 70 mutations in this gene have been identified in EPP families.^{426,430} In most symptomatic patients, inheritance of a second mutation is needed in order to reduce the enzymatic activity to a critical threshold where clinical symptoms are caused. Autosomal recessive inheritance has been demonstrated in 3% of patients with EPP.⁴²⁶

Management

The mainstay of management for EPP is sun avoidance and the use of physical sunscreens.^{431,432} Topical dihydroxyacetone may be helpful in some patients by producing brown pigment.³⁸⁶ Oral administration of β -carotene (30–90 mg/day for children) has been shown in uncontrolled studies to increase tolerance to sun exposure because it quenches the formation of free radicals.^{433–435} Narrowband ultraviolet B phototherapy has been proposed, as this wavelength does not cause photosensitivity.⁴³⁶

Patients with EPP should undergo frequent liver function tests, and those with persistent abnormalities should have a liver biopsy. Children with high erythrocyte protoporphyrins should have periodic determination of blood, urinary, and fecal porphyrins because increased excretion of coproporphyrins, high erythrocyte protoporphyrins and reduced excretion of fecal protoporphyrins can predict liver failure.⁴³³ Avoidance of drugs that interfere with hepatic excretory function is also essential.

Ancillary management strategies to minimize liver porphyrin accumulation including oral iron, intravenous hematin, transfusion therapy, and high-carbohydrate diet have been instigated, but their efficacy is unproven.⁴³³ Cholestyramine or activated charcoal have been used to interrupt the enterohepatic circulation of protoporphyrins.⁴³⁷ GI consultation is recommended for those with liver enzyme elevations. During surgical procedures, modification of lighting in the operating room may be needed to avoid phototoxicity to exposed organs.

HEPATOERYTHROPOIETIC PORPHYRIA

Hepatoerythropoietic porphyria (HEP) is an extremely rare disorder caused by a homozygous deficiency of uroporphyrinogen decarboxylase.^{438–441} Clinical manifestations begin in infancy, or more commonly in early childhood, and resemble both porphyria cutanea tarda and CEP. The disease usually presents with darkening of the urine and delayed-type cutaneous photosensitivity, with vesicles, skin fragility, milia, and scarring. With time, hypertrichosis, sclerodermoid changes, and mutilation similar to CEP become apparent. Anemia, hepatosplenomegaly, and abnormalities of liver function of varying degrees may also occur, but are less common than in CEP. The porphyrin excretion pattern resembles that of PCT, with elevated urinary uroporphyrins and 7-carboxylated porphyrins, and a smaller elevation of coproporphyrins, 6- and 5-carboxylated porphyrins. Increased isocoproporphyrins in feces are characteristic. Unlike in PCT, erythrocyte protoporphyrin is increased.

Treatment is similar to management for EPP.

OTHER PORPHYRIAS

Homozygous porphyrias

Other porphyrias with onset of symptoms in infancy or early childhood include homozygous variants of aminolevulinic acid dehydratase (ALAD) deficiency, homozygous coproporphyrin (harderoporphyria), homozygous variegate porphyria, and homozygous acute intermittent porphyria.^{442–451}

Transient porphyrinemias

Transient increases in porphyrin levels^{452–455} have been described in neonates with hemolytic disease of the newborn and in a neonate with severe liver failure due to tyrosinemia type 1.⁴⁵⁵ These infants develop erythema, violaceous discoloration, purpura, erosions, and blisters in areas exposed to phototherapy, with sharp demarcation at photoprotected sites. Sensitivity to sunlight may occur.

Elevated levels of plasma/urine porphyrins (mainly coproporphyrin) and/or erythrocyte protoporphyrin are found, which normalize spontaneously during the first few months. The cause of transient porphyrinemia is unclear but is probably due to cholestasis with accumulation of endogenous porphyrins. Other factors likely to be involved include blood transfusions and medications.

Xeroderma pigmentosum

Xeroderma pigmentosum (XP, MIM #278700) is an autosomal recessive disorder characterized by photosensitivity and early development of mucocutaneous cancer in sun-exposed areas. It is due to a defective DNA nucleotide excision repair (NER) after ultraviolet light-induced cellular injury. As NER also plays a role in normal nervous system development, some patients may show neurological impairment. Up to seven complementation groups and a variant subtype have been described to date. Most patients show symptoms within the first years of life. Severe sunburn with only minimal exposure to sunlight in an otherwise healthy infant may be the first clue to diagnosis. Other findings include early-onset excessive lentigines and freckling in sun-exposed areas, photophobia and conjunctivitis, early-onset actinic keratosis and melanoma and non-melanoma skin cancer. Rigorous protection against UVA and UVB radiation

from infancy is essential to minimize actinic damage in these patients (see [Chapter 24](#)).

Cockayne syndrome

Cockayne syndrome (CS, MIM #216400) is a rare autosomal recessive condition characterized by abnormal development that may become evident within the first few years after birth (type I), or early after birth (type II).⁴⁵⁶ CS shows some overlap with certain forms of XP.⁴⁵⁷ Clinical features include cutaneous photosensitivity, thin, dry hair, a progeroid appearance, progressive pigmentary retinopathy, mental retardation, sensorineural hearing loss, dental caries, and a characteristic 'horse-riding stance' in the ambulatory patient due to knee contractures.⁴⁵⁸ Patients with CS have no significant increase in skin cancer or infection, except in combined forms of XP-CS.⁴⁵⁸ Genetic studies have defined two Cockayne syndrome complementation groups: complementation group A owing to mutations of the CSA (*CKNI*, *ERCC8*), and complementation group B, owing to mutations of the CSB (*ERCC6*) genes.⁴⁵⁹ Exceptionally, mutations of genes for xeroderma pigmentosum (*XPB*, *XPD*, and *XPG*) result in a Cockayne syndrome phenotype (xeroderma pigmentosum–Cockayne syndrome complex).⁴⁵⁷

Trichothiodystrophy

Trichothiodystrophy (TTD, MIM #601675) is a rare, autosomal recessive syndromic ichthyosis, in which patients display a wide variety of clinical features, including cutaneous, neurological, and growth abnormalities. Depending on the clinical features of each patient, several acronyms have been used to describe the clinical features of these patients, including PIBIDS (photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature), IBIDS and BIDS.⁴⁶⁰ Photosensitivity is present only in 42% of cases, while hair abnormalities are constant.⁴⁶¹ The patients have sparse, easily breakable hair, with decreased sulfur or cysteine levels. Under polarizing microscopy, the hair displays a diagnostic alternating light and dark banding pattern, called 'tiger tail banding'.⁴⁶² TTD results from mutations in one of several different DNA repair genes (*XPB*, *XPD* or *TTDA*) and, in non-photosensitive TTD, *TTDN1*, a gene of unknown function. Although *XPB* and *XPD* mutations are also seen in xeroderma pigmentosum, TTD patients have not been reported to have an increased risk of cancer.

Ultraviolet-sensitive syndrome

This exceedingly rare autosomal recessive syndrome is due to UVSSA gene mutations.⁴⁶³ Clinically, it is characterized by cutaneous photosensitivity and mild freckling, without an increased risk of skin tumors.⁴⁶⁴ It is intimately related to Cockayne syndrome, as UVSSA mutations destabilize the ERCC6 complex.⁴⁶³

Rothmund–Thomson syndrome

Rothmund–Thomson syndrome (RTS, MIM #268400), is an autosomal recessive disorder characterized by photosensitivity and other findings. Erythema, edema and occasionally blistering can develop on the face, buttocks and extensor aspects of the limbs, usually before 2 years of age. Over time, the patients develop telangiectasias, skin atrophy and reticulated pigmentation (poikiloderma) both on sun-exposed and non sun-exposed areas with respect of trunk and abdomen ([Fig. 20.30](#)). Sparse, brittle, thin or absent scalp hair and sparse hair on eyelashes and/or eyebrows are frequently observed, as well as nail



Figure 20.30 Rothmund–Thomson syndrome. Poikilodermatous changes on the cheeks and extensor surfaces of the arms.

dystrophy, paronychia, and defective dentition.⁴⁶⁵ Approximately one-third of RTS patients present with hyperkeratosis on the hands, feet, knees, and elbows, as well as frank photosensitivity later in life. Growth delay and short stature is the second major clinical sign of RTS.⁴⁶⁶ Skeletal abnormalities are seen in up to two-thirds of the patients, including frontal bossing, saddle nose, and abnormalities of the long bones such as abnormal trabeculation, irregular metaphyses, osteoporosis and absent or malformed bones. Cataracts may be present in many patients with RTS.⁴⁶⁷ Gastrointestinal, hematological and pulmonary anomalies have been recorded sporadically.⁴⁶⁶ Intelligence is normal.

A predisposition to cancer is well-described, including osteosarcoma during childhood and squamous cell carcinoma of the skin (in adults).⁴⁶⁸ Isolated cases of melanoma have also been described.⁴⁶⁹ A defective *RECQL4* gene, a DNA helicase involved in DNA repair and genetic stability, is found in about 40–66% of patients.⁴⁷⁰

Bloom syndrome

Bloom syndrome (BS, MIM #210900), is an autosomal recessive disorder characterized by a sun-sensitive telangiectatic erythema with a 'butterfly distribution' on the cheeks and variably involving the nose, eyelids, forehead, ears and lips, present within the first weeks of life, followed by telangiectasias, atrophy and hyperpigmentation. Areas of hypopigmentation and café-au-lait macules have been described, especially on the trunk, as well as acanthosis nigricans.⁴⁷¹ However, the hallmark of the syndrome is the consistent proportionate pre- and postnatal growth retardation accompanied by dolichocephaly, and a predisposition to a wide variety of epithelial malignancies such as colon, breast and lung cancer, hematological neoplasias, sarcomas, and rare pediatric tumors, including Wilms tumors.⁴⁷² Deficient cellular and humoral immunity is common and explains recurrent infections (otitis media and pneumonia). Chronic pulmonary disease, diabetes mellitus and learning disabilities are common. BS is due to mutations in *RECQL3*, a DNA helicase, resulting in chromosomal instability.

Kindler syndrome

Kindler syndrome (MIM #173650), is now considered a subtype of epidermolysis bullosa (see [Chapter 11](#)). It is an autosomal

recessive condition characterized by blistering at birth, photosensitivity, and progressive poikiloderma.⁴⁷³ Patients also show mucosal involvement and increased incidence of epithelial skin cancer.⁴⁷⁴ It is due to mutations in the *FERMT1* gene, which encodes the focal adhesion protein kindlin-1.⁴⁷⁵

Smith–Lemli–Opitz syndrome

Smith–Lemli–Opitz Syndrome (SLOS, MIM #270400) is an autosomal recessive disorder characterized by distinctive facial features, microcephaly, polydactyly, 2–3 toe syndactyly, hypospadias, and variable degree of neurological impairment.⁴⁷⁶ Photosensitivity appears in 57% of patients,⁴⁷⁷ who show sunburn-like erythema after minimal sun exposure but lack pigmentary lesions, poikiloderma or increased risk of skin cancer. It is due to an inborn error of cholesterol synthesis secondary to a deficiency of 7-dehydrocholesterol reductase.^{478,479} The clinical spectrum is wide, and rare individuals have been described with normal development and only minor malformations.

Hartnup disease

Hartnup disease (MIM #234500) is an autosomal recessive disorder characterized by photo-sensitive rash, cerebellar ataxia, emotional instability and aminoaciduria. It is due to a defect in the transport of tryptophan and other neutral amino acids across the epithelial cells in the kidneys and gastrointestinal tract that leads to a decrease in the synthesis of nicotinamide. The gene responsible for the disease has been mapped to chromosome 5p15 that encodes the transporter protein SLC6A19.^{480,481} It clinically manifests as a dietary niacin deficiency (pellagra), showing photodistributed scaly erythematous plaques, cheilitis, diarrhea and neurological impairment.⁴⁸² Laboratory tests demonstrate increased levels of neutral aminoacid metabolites and tryptophan in urine.⁴⁸³ Avoidance of sun exposure and treatment with nicotinic acid or nicotinamide are required.

Purpura and petechiae in infants and newborns

Purpura in the neonate is almost always an emergency and should prompt an immediate search for an underlying disorder. In infants, however, purpura may have a benign etiology, especially when it is not associated with fever.⁴⁸⁴ Infectious causes of purpura in newborns and young infants, such as meningococcal sepsis and others are discussed elsewhere in this book.

PURPURA IN NEONATES

Apart from trauma, purpura in the newborn may be due to coagulation defects, platelet abnormalities, or infections (Box 20.5). Extramedullary erythropoiesis also causes purpuric lesions. In evaluating the neonate or infant with purpura it is important to obtain a maternal and familial history of bleeding diathesis and thromboembolic phenomena, medication intake, and symptoms of infectious diseases. In neonates, a general physical examination and workup for sepsis is warranted. Laboratory studies should include hemoglobin and hematocrit values, platelet count, white blood count, coagulation studies, and TORCH serologies.

BOX 20.5 DIFFERENTIAL DIAGNOSIS OF NEONATAL PURPURA

1. Extramedullary erythropoiesis ('blueberry muffin' baby)
2. Coagulation defects
 - Protein C and S deficiency (neonatal purpura fulminans)
 - Hemorrhagic disease of the newborn
 - Hereditary clotting factor deficiencies
3. Platelet abnormalities
 - a. Immune platelet destruction
 - Alloimmune neonatal thrombocytopenia
 - Maternal autoimmune thrombocytopenia (ITP, lupus)
 - Drug-related immune thrombocytopenia
 - b. Primary platelet production/function defects
 - Thrombocytopenia with absent radii syndrome
 - Wiskott–Aldrich syndrome
 - Fanconi anemia
 - Congenital megakaryocytic thrombocytopenia
 - X-linked recessive thrombocytopenia
 - Other hereditary thrombocytopenias
 - Giant platelet syndromes (Bernard–Soulier, May–Hegglin)
 - Trisomy 13 or 18
 - Alport syndrome variants
 - Gray platelet syndrome
 - Glanzmann thrombasthenia
 - c. Kasabach–Merritt syndrome^a
4. Infections^b
 - Congenital (TORCH)
 - Sepsis
 - HIV
 - Parvovirus B19
5. Trauma
6. Purpuric phototherapy-induced eruption

^aBoth thrombocytopenia and consumption coagulopathy are involved in the pathogenesis.

^bInfection may cause purpura by several mechanisms.

(Modified from Baselga E, Drolet BA, Esterly NB. *J Am Acad Dermatol* 1997; 37:673–705.)

DERMAL ERYTHROPOIESIS (BLUEBERRY MUFFIN BABY)

Persistence of the erythropoietic activity of fetal dermal mesenchyme into the newborn period produces a characteristic purpuric eruption for which the term 'blueberry muffin baby' was coined. The eruption, first observed in newborns with congenital rubella (Fig. 20.31), may be the result of other intrauterine infections (Fig. 20.32) and hematologic dyscrasias with chronic and severe anemia.^{485–487} However, it is now appreciated that dermal erythropoiesis can occur with non-infectious causes, particularly those that result in fetal anemia.^{401,488,489} Conversely, many other conditions that resemble this phenotype can occur with conditions other than dermal erythropoiesis, mainly dermal metastatic infiltration by congenital malignancies and vascular lesions (Fig. 20.33).⁴⁹⁰

Cutaneous and extracutaneous findings

The cutaneous lesions of blueberry muffin babies consist of dark blue or magenta, nonblanchable, round to oval papules ranging in size from 1 to 7 mm and have a generalized distribution, with emphasis on the head, neck, and trunk (Fig. 20.34). The papules are firm to palpation, with an infiltrative quality that distinguishes them from petechiae and purpura, which often coexist in the same patient. These lesions evolve into dark purple to brown macules and involute spontaneously within



Figure 20.31 (A) Infant with congenital rubella and 'blueberry muffin' lesions. (B) Purple papules and hepatomegaly in a neonate with congenital CMV.



Figure 20.32 'Blueberry muffin' lesions associated with cytomegalic inclusion disease.



Figure 20.33 Infiltration of the skin by leukemia cutis producing a blueberry muffin appearance.



Figure 20.34 Lesions of dermal erythropoiesis in an infant with Rh incompatibility due to RhoGAM failure.

2–6 weeks. Blueberry muffin lesions caused by infiltrative processes are usually larger, more nodular, less hemorrhagic, fewer in number, and firmer to palpation. Accompanying abnormalities vary with the underlying cause.

Etiology and pathogenesis

In the prevaccination era, rubella was the most common cause of dermal erythropoiesis, but congenital cytomegalovirus (CMV) infection is now the major cause.^{485,486} Dermal erythropoiesis has been associated with other intrauterine infections, such as coxsackie B2,⁴⁸⁵ and parvovirus B19,⁴⁹¹ as well as hematologic dyscrasias such as Rh incompatibility (Fig. 20.34),⁴⁹² maternofetal ABO incompatibility,⁴⁸⁵ spherocytosis,⁴⁹³ and the twin transfusion syndrome (Box 20.6). In rare instances, it may occur in otherwise healthy newborns.⁴⁸⁵ Dermal erythropoiesis with late-onset blueberry muffin lesions has also been described as a side-effect of recombinant erythropoietin in a premature infant.⁴⁹⁴

Laboratory tests and histopathology

Histopathologic examination demonstrates poorly circumscribed collections of nucleated and nonnucleated red blood cells, predominantly confined to the reticular dermis and

BOX 20.6 DIFFERENTIAL DIAGNOSIS OF BLUEBERRY MUFFIN LESIONS**DERMAL ERYTHROPOIESIS**

- Congenital infection
 - Rubella
 - Cytomegalovirus
 - Parvovirus B19
 - Coxsackievirus B2
- Hemolytic disease of the newborn
 - Rh incompatibility
 - Blood group incompatibility
- Hereditary spherocytosis
- Twin transfusion syndrome

NEOPLASTIC-INFILTRATIVE DISEASES

- Neuroblastoma
- Rhabdomyosarcoma
- Langerhans' cell histiocytosis

CONGENITAL LEUKEMIA

(Modified from Baselga E, Drolet BA, Esterly NB. *J Am Acad Dermatol* 1997; 37:673–705.)

BOX 20.7 CAUSES OF PURPURA FULMINANS IN NEWBORNS AND YOUNG INFANTS**CONGENITAL/INHERITED CONDITIONS**

- Homozygous protein C deficiency
- Homozygous protein S deficiency

ACQUIRED CAUSES

- Increased consumption or clearance of protein C or S
 - Severe sepsis (e.g., group B *Streptococcus*, meningococcal)
 - Post-infectious purpura fulminans (after chickenpox or streptococcal infection)
 - Disseminated intravascular coagulation
 - Acute venous thrombosis
 - Cardiac bypass
- Decreased synthesis of protein C or S
 - Severe hepatic dysfunction
 - Galactosemia
 - Severe congenital heart disease
 - Warfarin therapy

(Modified from Price VE, Ledingham DL, Krümpel A, Chan AK. *Diagnosis and management of neonatal purpura fulminans. Semin Fetal Neonatal Med* 2011; 16:318–322.)

extending to the subcutaneous tissue.^{485–487} Occasionally, a few myeloid precursors may be interspersed.

Laboratory findings depend on the underlying cause. In the evaluation of a blueberry muffin baby the following tests are indicated: peripheral blood count, hemoglobin level, TORCH serologies, viral cultures, and a Coombs' test. Skin biopsy is not always necessary for diagnosis, but if a clear-cut cause is not evident, should be performed to exclude another diagnosis.

Differential diagnosis

The differential diagnosis includes other causes of neonatal purpura, such as coagulation defects, platelet abnormalities, and infections. Neoplastic diseases that produce infiltrative metastases in the neonatal period, such as neuroblastomas,^{495–497} rhabdomyosarcomas,⁴⁹⁸ myelogenous leukemias,⁴⁹⁹ and Langerhans' cell histiocytosis, especially the congenital self-healing reticulohistiocytosis variant (Hashimoto–Pritzker),⁵⁰⁰ should be considered.⁴⁹⁰ Newborns with multifocal lymphangioendotheliomatosis with thrombocytopenia or blue rubber bleb nevus syndrome may also have the appearance of a blueberry muffin baby.⁴⁹⁰

Course, management, treatment, and prognosis

The lesions of true dermal erythropoiesis fade and resolve spontaneously 3–6 weeks after birth. Treatment is directed at the underlying condition.

PURPURA FULMINANS IN NEWBORNS AND YOUNG INFANTS

Purpura fulminans is a clinico-pathological entity characterized by massive and progressive hemorrhagic necrosis of the skin accompanied by thrombosis of the cutaneous vasculature.

In newborns and young infants, there are both congenital and acquired causes (Box 20.7). Congenital inherited cases are due to homozygous deficiency of protein C or protein S. Acquired causes are more common, and are associated with

increased consumption or relative deficiency of protein C or S.⁵⁰¹ Purpura fulminans in severe sepsis (such as meningococemia) is the result of a local defect in the activation of protein C on small vessel endothelial cells,⁵⁰² whereas post-infectious purpura fulminans, usually occurring after chickenpox or streptococcal infections, is due to decreased protein S activity caused by cross-reacting IgG autoantibodies.⁵⁰²

CONGENITAL PROTEINS C AND S DEFICIENCIES

Congenital purpura fulminans is usually the result of inherited thrombophilic disorders that are attributable to protein C deficiency, protein S deficiency, or resistance to activated protein C due to factor V mutations.

Cutaneous findings

Congenital purpura fulminans manifests 2–12 hours after birth. In rare instances, delayed onset of up to 6–10 months of age has been described.⁵⁰³ Cutaneous lesions consist of extensive ecchymoses in a diffuse and often symmetric distribution that rapidly evolve into hemorrhagic bullae and purple-black necrotic skin lesions, which ultimately form a thick eschar (Fig. 20.35). The initial ecchymotic areas are sharply defined from the surrounding skin and usually have a red, advancing inflammatory rim. They are most common at sites of trauma or pressure, the buttocks, extremities, trunk, and scalp. Mucous membranes may rarely be involved.⁵⁰⁴ If treatment is instituted in the first 1–3 hours, before necrosis ensues, the initial lesions may be reversible.⁵⁰⁵

Extracutaneous findings

Other organs may be affected by the microvascular thrombosis, most commonly the CNS and eye, but also the kidney and gastrointestinal tract. Cavernous sinus involvement, which may occur in utero, can result in hydrocephalus, seizures, intracerebral hemorrhage, and mental retardation.^{506–508}



Figure 20.35 Neonatal purpura fulminans due to protein C deficiency.

Microphthalmia, cataracts, and blindness due to vitreous or retinal hemorrhage may be seen.^{506,509} Deep venous thrombosis and pulmonary embolism have also been described.⁵⁰⁷

Etiology and pathogenesis

Congenital purpura fulminans is almost always caused by inherited thrombophilic states such as homozygous protein C and S deficiency or resistance to activated protein C. Severe bacterial infection associated with DIC can also induce purpura fulminans in the neonate, although it is more common in infancy or early childhood.^{510,511} Proteins C and S are vitamin K-dependent glycoproteins with antithrombotic properties.^{512,513}

Protein C deficiency is an autosomal dominant disease with incomplete penetrance.⁵¹³ Homozygous or compound heterozygous patients have a severe clinical phenotype and usually present with neonatal purpura fulminans, although they may be asymptomatic or present later in life with recurrent thrombosis.^{514,515}

Protein S deficiency is also transmitted as an autosomal dominant trait with incomplete penetrance.⁵¹³ Homozygous patients may develop neonatal purpura fulminans, although the risk is lower than in patients with homozygous protein C deficiency.^{516,517}

Neonatal purpura fulminans may also be caused by activated protein C resistance due to a mutation in the factor V gene.^{504,518} Resistance to activated protein C may coexist with protein S and protein C deficiencies, becoming an additional genetic risk factor for purpura fulminans or thromboembolic complications, and explaining in part the incomplete clinical penetrance of inherited thrombophilic disorders.⁵¹⁹

Laboratory tests and histopathology

Blood coagulation studies demonstrate evidence of DIC, including prolonged prothrombin and partial thromboplastin times, increased fibrin split products, reduced fibrinogen, and reduced platelets. Microangiopathic hemolytic anemia may occur.

Biopsy of the early skin lesions demonstrates occlusion of dermal blood vessels by microthrombi. Hemorrhage and dermal necrosis are present in the more advanced stages. Necrosis of the overlying epidermis with subepidermal hemorrhagic bullae occurs in later phases. Secondary fibrinoid necrosis of dermal

vessel walls may be present in the necrotic areas, but primary vasculitis is absent.^{505,520}

A definitive diagnosis of protein C and S deficiency is established by measurements of protein C and S levels.⁵¹³ Protein C deficiencies can be identified by immunoenzymatic assays measuring the actual concentration of the protein in plasma, and two functional assays measuring the enzymatic activity and the anticoagulant activity. These tests distinguish two types of protein C deficiency. In type I, which is the most common, reduced synthesis of the normal protein leads to a low plasma concentration in all three assays. In type II, a qualitative deficiency, levels are normal but functional assays are abnormal. For protein S deficiency, functional and immunoenzymatic assays are available, and both the free form and the inactive form that circulates bound to C4b-binding protein have to be measured.⁵¹³ Type I deficiency is characterized by low total and free protein S, type II by normal free protein S and low activity, and type III by low free protein levels with normal total levels.

Interpreting the results of the assays may be difficult because protein C and S levels are physiologically reduced in the neonatal period, and may be undetectable in sick newborns with liver disease, respiratory distress syndrome, DIC, or sepsis.^{505,509–511,521} A complete sepsis workup is therefore recommended in any case of neonatal purpura fulminans. Serial determination of protein levels in patients and other family members is necessary to exclude a transient deficiency and confirm true congenital deficiency.

Differential diagnosis

The cutaneous lesions of purpura fulminans are very characteristic and rarely mistaken for any other condition. Other causes of purpuric eruptions in the newborn may be considered (Box 20.5).

Course, management, treatment, and prognosis

Without treatment, congenital purpura fulminans is often fatal. If the diagnosis is suspected, therapy should be initiated immediately without waiting for the results of protein C and S measurements. Prompt treatment may completely reverse early skin lesions. Initial therapy consists of the administration of fresh frozen plasma (10–15 mL/kg per 12 h) or prothrombin complex concentrate, sources of protein C, protein S, and activated protein C.^{509,505} A protein C concentrate has been developed that has the advantage of avoiding blood volume overload and does not carry the risk of transmission of viral diseases.^{522,523} Protein S concentrate is not yet available for clinical use. Replacement therapy should be continued until all lesions have healed, usually after 4–8 weeks. Long-term treatment involves careful administration of oral anticoagulants, starting at very low doses and with protective replacement therapy to avoid coumarin-induced skin necrosis. Experience with long-term treatment using protein C infusions is limited.⁵⁰² There are few case reports of a successful liver transplant for homozygous protein C deficiency.^{524,525}

PURPURIC PHOTOTHERAPY-INDUCED ERUPTION

This benign, transient purpura in transfused neonates who undergo phototherapy is characterized by raspberry-colored,

nonblanching lesions at exposed sites, sparing sites that are protected from lights (e.g., leads and temperature probes).^{288,271} The eruption develops after 1–4 days of phototherapy and clears spontaneously after discontinuation of light therapy. Histologically, there is extravasation of red blood cells in the dermis without epidermal damage. The pathogenesis of this disease is unknown, although transient porphyria has been detected in some patients.^{454,526} The purpuric nature of the eruption and the absence of ‘sunburn cells’ differentiate this eruption from ‘sunburn’ caused by exposure to UVA from fluorescent lamps.⁵²⁷ Congenital erythropoietic porphyria and transient elevated porphyrin levels in neonates with hemolytic disease may also cause photosensitivity.⁵²⁶ Drug-induced phototoxicity in neonates who have received photosensitizing chemicals such as fluorescein dye, furosemide, or methylene-blue must be considered.^{384,385,528,529}

PIGMENTED PURPURIC ERUPTIONS (PPE)

The pigmented purpuric eruptions, also called chronic pigmented purpura (CPP), share the common features of chronic blood extravasation due to capillaritis of the dermis. PPE is rare in young infants; only a few cases with onset in infancy have been reported,⁵³⁰ but onset in newborns and infants is exceptional.⁵³¹ The most common of these is Schamberg disease characterized by pinhead purpuric macules, that then evolve to patches comprised of red-brown areas which often contain so-called ‘cayenne pepper spots’. Another form is more annular – so-called ‘Majocchi purpura annularis telangiectodes’. An eczematous form, is so-called ‘purpura of Doucas and Kapetanakis’. Lichen aureus may have slightly elevated lesions, which have a yellow-gold hue. Another form, Gougerot–Blum, has more infiltrated purpuric plaques. A familial form of the disease has been reported.⁵³²

Skin lesions are often located on the lower extremities but the upper limbs and trunk can be affected as well. A bilateral distribution is common, although unilateral and even segmental distribution is well recognized.⁵³³ The condition may wax and wane for months to years.

Chronic pigmented purpura (CPP) is typically a disease of adults. It has also however, been shown to appear in children.

The diagnosis of CPP should be confirmed on skin biopsy. Results depend on the subtype but all share in common perivascular inflammation with hemosiderin deposition, but special immunohistochemical stains are sometimes needed to

demonstrate these findings. In uncertain cases, other causes of petechiae and purpura must be excluded. A blood cell count, platelet count, and clotting studies are indicated, and must show normal results.

CPP is usually a benign and indolent condition. However, a CPP-like eruption can be a prodrome of linear morphea,⁵³⁴ and very occasionally, skin lymphoma may mimic CPP.⁵³⁵ Treatment of CPP is usually unsatisfactory. Different modalities, such as topical steroids, griseofulvin, pentoxifylline, PUVA, and oral vitamin C and rutoside have variable responses.⁵³⁶

PETECHIAE AND PETECHIAL ERUPTIONS


There are many other potential causes of purpura and petechiae in young infants, and they do not necessarily imply a poor prognosis or an ominous situation. Many infants with purpura attend emergency departments, where they have extensive investigations, but their outcomes are benign. These ‘benign’ purpuric eruptions include mechanical causes, viral illnesses, or others.⁴⁸⁴

In other cases, purpura can be a consequence of vascular damage, as is the case in blood extravasation from active erythema (urticaria with secondary purpura, urticaria multiforme), polyarteritis nodosa, infectious emboli, pyoderma gangrenosum, fatty tissue inflammation (panniculitis), or vascular spasm (livedoid necrosis of Nicolau–Freudenthal). Platelet and clotting disorders can also take the form of purpura, and need to be evaluated. In Wiskott–Aldrich disease, both thrombocytopenia and autoimmune phenomena leading to vasculitis are potential causes of purpura as an early manifestation.³⁴⁷

Finally, a purpuric component in skin lesions may be an important clue to the diagnosis of a potentially serious skin disease, as is the case of purpuric papules in Langerhans’ cell histiocytosis. On the other hand, less serious skin diseases can appear with prominent purpura, such as pityriasis lichenoides, pityriasis rosea or eczema.

Access the full reference list at [ExpertConsult.com](https://www.expertconsult.com) 

Figure 23 is available online at [ExpertConsult.com](https://www.expertconsult.com) 

Table 9 is available online at [ExpertConsult.com](https://www.expertconsult.com) 

Box 4 is available online at [ExpertConsult.com](https://www.expertconsult.com) 

KEY REFERENCES

68. Hon KL, Leung AK. Neonatal lupus erythematosus. *Autoimmune Dis* 2012;2012:301274.
86. Carder KR. Hypersensitivity reactions in neonates and infants. *Dermatol Ther* 2005;18(2):160–75.
126. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens–Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 2002;138(8):1019–24.
169. Pite H, Wedi B, Borrego LM, et al. Management of childhood urticaria: current knowledge and practical recommendations. *Acta Derm Venereol* 2013;93(5):500–8.
181. Savic S, Dickie LJ, Wittmann M, et al. Autoinflammatory syndromes and cellular responses to stress: pathophysiology, diagnosis and new treatment perspectives. *Best Pract Res Clin Rheumatol* 2012;26:505–33.
269. Yim D, Curtis N, Cheung M, Burgner D. An update on Kawasaki disease II: clinical features, diagnosis, treatment and outcomes. *J Paediatr Child Health* 2013;49(8):614–23.
359. Chantorn R, Lim HW, Shwayder TA. Photosensitivity disorders in children: part II. *J Am Acad Dermatol* 2012;67(6):1113 e1–15; quiz 28, 27.
360. Chantorn R, Lim HW, Shwayder TA. Photosensitivity disorders in children: part I. *J Am Acad Dermatol* 2012;67(6):1093 e1–18; quiz 111–2.
484. Lee MH, Barnett PL. Petechiae/purpura in well-appearing infants. *Pediatr Emerg Care* 2012;28:503–5.
490. Holland KE, Galbraith SS, Drolet BA. Neonatal violaceous skin lesions: expanding the differential of the ‘blueberry muffin baby’. *Adv Dermatol* 2005;21:153–92.

REFERENCES

- Bressler GS, Jones RE, Jr. Erythema annulare centrifugum. *J Am Acad Dermatol* 1981;4: 597–602.
- Harrison PV. The annular erythemas. *Int J Dermatol* 1979;18:282–90.
- Toledo-Alberola F, Betloch-Mas I. Annular erythema of infancy. *Actas Dermosifiliogr* 2010;101:473–84.
- Cox NH, McQueen A, Evans TJ, et al. An annular erythema of infancy. *Arch Dermatol* 1987;123:510–13.
- Puig L, Moreno A, Alomar A, et al. Erythema gyratum atrophicans transiens neonatale: a variant of cutaneous neonatal lupus erythematosus. *Pediatr Dermatol* 1988;5:112–16.
- Ashurst PJ. Erythema annulare centrifugum due to hydroxychloroquine sulfate and chloroquine sulfate. *Arch Dermatol* 1967;95:37–9.
- Toonstra J, de Wit RE. 'Persistent' annular erythema of infancy. *Arch Dermatol* 1984;120: 1069–72.
- Hebert AA, Esterly NB. Annular erythema of infancy. *J Am Acad Dermatol* 1986;14:339–43.
- Patrizi A, Savoia F, Varotti E, et al. Neutrophilic figurate erythema of infancy. *Pediatr Dermatol* 2008;25:255–60.
- Wong LC, Kakakios A, Rogers M. Congenital annular erythema persisting in a 15-year-old girl. *Australas J Dermatol* 2002;43:55–61.
- Bottoni U, Innocenzi D, Bonaccorsi P, et al. Erythema annulare centrifugum: report of a case with neonatal onset. *J Eur Acad Dermatol Venereol* 2002;16:500–3.
- Howes R, Girgis L, Kossard S. Eosinophilic annular erythema: a subset of Wells syndrome or a distinct entity? *Australas J Dermatol* 2008;49:159–63.
- Gianotti F, Ermacora E. Erythema gyratum atrophicans transiens neonatale. *Arch Dermatol* 1975;111:615–16.
- Tyring SK. Reactive erythemas: erythema annulare centrifugum and erythema gyratum repens. *Clin Dermatol* 1993;11:135–9.
- Guillet MH, Dorval JC, Larregue M, Guillet G. Erythema annulare centrifuge de Darier à debut neonatal avec 15 ans de suivi. Efficacité de l'interféron et rôle de cytokines. *Ann Dermatol Venereol* 1995;122:422–6.
- Hammar H. Erythema annulare centrifugum coincident with Epstein-Barr virus infection in an infant. *Acta Paediatr Scand* 1974;63: 788–92.
- Schmid MH, Wollenberg A, Sander CA, et al. Erythema annulare centrifugum and intestinal *Candida albicans* infection – coincidence or connection? *Acta Derm Venereol* 1997;77: 93–4.
- Hendricks AA, Lu C, Elfenbein GJ, et al. Erythema annulare centrifugum associated with ascariasis. *Arch Dermatol* 1981;117:582–5.
- Shelley WB. Erythema annulare centrifugum. A case due to hypersensitivity to blue cheese penicillium. *Arch Dermatol* 1964;90:54–8.
- Kavurt S, Aydemir O, Celik U, et al. Erythema annulare centrifugum as the presenting sign of *Pseudomonas aeruginosa* sepsis in a newborn. *Eur J Pediatr* 2013;172:847–9.
- Weyers W, Diaz-Cascajo C, Weyers I. Erythema annulare centrifugum: results of a clinicopathologic study of 73 patients. *Am J Dermatopathol* 2003;25:451–62).
- Watsky KL, Hansen T. Annular erythema in identical twins. *Cutis* 1989;44:139–40.
- Beare JM, Froggatt P, Jones JH, Neill DW. Familial annular erythema. An apparently new dominant mutation. *Br J Dermatol* 1966;78:59–68.
- Williams C, Merchant WJ, Clark SM. Familial annular erythema – a rare dermatology diagnosis. *Pediatr Dermatol* 2011;28(1):56–8.
- Kikuchi I, Ogata K, Inoue S. Pityrosporum infection in an infant with lesions resembling erythema annulare centrifugum. *Arch Dermatol* 1984;120:380–2.
- Trevisan G, Stinco G, Cinco M. Neonatal skin lesions due to a spirochetal infection: a case of congenital Lyme borreliosis? *Int J Dermatol* 1997;36:677–80.
- Lee LA. Neonatal lupus erythematosus. *J Invest Dermatol* 1993;100:9S–13S.
- Lee LA. Neonatal lupus: clinical features, therapy, and pathogenesis. *Curr Rheumatol Rep* 2001;3:391–5.
- Lee LA. Neonatal lupus erythematosus: clinical findings and pathogenesis. *J Invest Dermatol Symp Proc* 2004;9:52–6.
- Silverman ED, Laxer RM. Neonatal lupus erythematosus. *Rheum Dis Clin North Am* 1997;23:599–618.
- Watson RM, Lane AT, Barnett NK, et al. Neonatal lupus erythematosus. A clinical, serological and immunogenetic study with review of the literature. *Medicine (Baltimore)* 1984;63: 362–78.
- Buyon JP, Clancy RM. Neonatal lupus: basic research and clinical perspectives. *Rheum Dis Clin North Am* 2005;31:299–313.
- Weston WL, Morelli JG, Lee LA. The clinical spectrum of anti-Ro-positive cutaneous neonatal lupus erythematosus. [Abstract]. *J Am Acad Dermatol* 1999;40:675–81.
- Neiman AR, Lee LA, Weston WL, et al. Cutaneous manifestations of neonatal lupus without heart block: characteristics of mothers and children enrolled in a national registry. [Abstract]. *J Pediatr* 2000;137:674–80.
- Sheth AP, Esterly NB, Ratoosh SL, et al. U1RNP positive neonatal lupus erythematosus: association with anti-La antibodies? *Br J Dermatol* 1995;132:520–6.
- Provost TT, Watson R, Gammon WR, et al. The neonatal lupus syndrome associated with U1RNP (nRNP) antibodies. *N Engl J Med* 1987;316:1135–8.
- Diociaiuti A, Paone C, Giraldo L, et al. Congenital lupus erythematosus: case report and review of the literature. *Pediatr Dermatol* 2005;22:240–2.
- Elish D, Silverberg NB. Neonatal lupus erythematosus. *Cutis* 2006;77:82–6.
- Nakajima K, Wakiguchi H, Kodama H, et al. Neonatal lupus erythematosus in identical twins, showing transient bullous lesions. *Pediatr Dermatol* 2011;28:397–400.
- Miyagawa S. Neonatal lupus erythematosus: a review of the racial differences and similarities in clinical, serological and immunogenetic features of Japanese versus Caucasian patients. *J Dermatol* 2005;32:514–22.
- Nitta Y. Lupus erythematosus profundus associated with neonatal lupus erythematosus. *Br J Dermatol* 1997;136:112–14.
- Crowley E, Frieden IJ. Neonatal lupus erythematosus: an unusual congenital presentation with cutaneous atrophy, erosions, alopecia, and pancytopenia. *Pediatr Dermatol* 1998;15: 38–42.
- Cimaz R, Biggioggero M, Catelli L, et al. Ultra-violet light exposure is not a requirement for the development of cutaneous neonatal lupus. *Lupus* 2002;11:257–60.
- See A, Wargon O, Lim A, et al. Neonatal lupus erythematosus presenting as papules on the feet. *Australas J Dermatol* 2005;46:172–6.
- Thornton CM, Eichenfield LF, Shinnall EA, et al. Cutaneous telangiectases in neonatal lupus erythematosus. *J Am Acad Dermatol* 1995;33: 19–25.
- Wisuthsarewong W, Soongswang J, Chantorn R. Neonatal lupus erythematosus: clinical character, investigation, and outcome. *Pediatr Dermatol* 2011;28:115–21.
- Vilchez-Márquez F, Martín-Fuentes A, Conejero R, et al. Neonatal lupus erythematosus mimicking extensive capillary malformation. *Pediatr Dermatol* 2012; Jan 26, doi: 10.1111/j.1525-4702.2011.01676.x. [Epub ahead of print].
- Fritz M, Vats K, Goyal RK. Neonatal lupus and IUGR following alpha-interferon therapy during pregnancy. *J Perinatol* 2005;25:552–4.
- Geggel RL, Tucker L, Szer I. Postnatal progression from second- to third-degree heart block in neonatal lupus syndrome. *J Pediatr* 1988;113: 1049–52.
- Hornberger LK, Al Rajaa N. Spectrum of cardiac involvement in neonatal lupus. *Scand J Immunol* 2010;72:189–97.
- Lee LA, Sokol RJ, Buyon JP. Hepatobiliary disease in neonatal lupus: prevalence and clinical characteristics in cases enrolled in a national registry. *Pediatrics* 2002;109:E11.
- Cimaz R, Spence DL, Hornberger L, et al. Incidence and spectrum of neonatal lupus erythematosus: a prospective study of infants born to mothers with anti-Ro autoantibodies. *J Pediatr* 2003;142:678–83.
- Schecher LE, Kasteler JS, Callen JP. Neonatal lupus erythematosus mimicking Langerhans' cell histiocytosis. *Pediatr Dermatol* 2003;20: 164–6.
- Kanagasegar S, Cimaz R, Kurien BT, et al. Neonatal lupus manifests as isolated neutropenia and mildly abnormal liver functions. *J Rheumatol* 2002;29:187–91.
- Watson R, Kang JE, May M, et al. Thrombocytopenia in the neonatal lupus syndrome. *Arch Dermatol* 1988;124:560–3.
- Bourke JE, Burns DA. Neonatal lupus erythematosus with persistent telangiectasia and spastic paraparesis. *Clin Exp Dermatol* 1993;18:271–3.
- Rider LG, Sherry DD, Glass ST. Neonatal lupus erythematosus simulating transient myasthenia gravis at presentation. *J Pediatr* 1991;118: 417–19.
- Contractor S, Hiatt M, Kosmin M, et al. Neonatal thrombosis with anticardiolipin antibody in baby and mother. *Am J Perinatol* 1992;9:409–10.
- Prendiville JS, Cabral DA, Poskitt KJ, et al. Central nervous system involvement in neonatal lupus erythematosus. *Pediatr Dermatol* 2003;20:60–7.
- Silverman E, Jaeggi E. Non-cardiac manifestations of neonatal lupus erythematosus. *Scand J Immunol* 2010;72:223–5.
- Lawrence S, Luy L, Laxer R, et al. The health of mothers of children with cutaneous neonatal lupus erythematosus differs from that of

- mothers of children with congenital heart block. *Am J Med* 2000;108:705–9.
62. Julkunen H, Eronen M. Long-term outcome of mothers of children with isolated heart block in Finland. *Arthritis Rheum* 2001;44:647–52.
 63. Brucato A, Franceschini F, Gasparini M, et al. Isolated congenital complete heart block: long-term outcome of mothers, maternal antibody specificity and immunogenetic background. *J Rheumatol* 1995;22:533–40.
 64. McCune AB, Weston WL, Lee LA. Maternal and fetal outcome in neonatal lupus erythematosus. *Ann Intern Med* 1987;106:518–23.
 65. Brucato A, Franceschini F, Buyon JP. Neonatal lupus: long-term outcomes of mothers and children and recurrence rate. *Clin Exp Rheumatol* 1997;15:467–73.
 66. Press J, Uziel Y, Laxer RM, et al. Long-term outcome of mothers of children with complete congenital heart block. *Am J Med* 1996;100:328–32.
 67. Buyon JP, Kim MY, Copel JA, et al. Anti-Ro/SSA antibodies and congenital heart block: necessary but not sufficient. *Arthritis Rheum* 2001;44:1723–7.
 68. Hon KL, Leung AK. Neonatal lupus erythematosus. *Autoimmune Dis* 2012;2012:301274.
 69. Gordon P, Khamashta MA, Rosenthal E, et al. Anti-52 kDa Ro, anti-60 kDa Ro, and anti-La antibody profiles in neonatal lupus. *J Rheumatol* 2004;31:2480–7.
 70. Silverman ED, Buyon J, Laxer RM, et al. Auto-antibody response to the Ro/La particle may predict outcome in neonatal lupus erythematosus. *Clin Exp Immunol* 1995;100:499–505.
 71. Stevens AM, Hermes HM, Lambert NC, et al. Maternal and sibling microchimerism in twins and triplets discordant for neonatal lupus syndrome-congenital heart block. *Rheumatology (Oxford)* 2005;44:187–91.
 72. Cruz RB, Viana VS, Nishioka SA, et al. Is isolated congenital heart block associated to neonatal lupus requiring pacemaker a distinct cardiac syndrome? *Pacing Clin Electrophysiol* 2004;27:615–20.
 73. Costedoat-Chalumeau N, Amoura Z, Lupoglazoff JM, et al. Outcome of pregnancies in patients with anti-SSA/Ro antibodies: a study of 165 pregnancies, with special focus on electrocardiographic variations in the children and comparison with a control group. *Arthritis Rheum* 2004;50:3187–94.
 74. Taylor-Albert E, Reichlin M, Toews WH, et al. Delayed dilated cardiomyopathy as a manifestation of neonatal lupus: case reports, autoantibody analysis, and management. *Pediatrics* 1997;99:733–5.
 75. Moak JP, Barron KS, Hougen TJ, et al. Congenital heart block: development of late-onset cardiomyopathy, a previously underappreciated sequela. *J Am Coll Cardiol* 2001;37:238–42.
 76. Martin V, Lee LA, Askanase AD, et al. Long-term followup of children with neonatal lupus and their unaffected siblings. *Arthritis Rheum* 2002;46:2377–83.
 77. Buyon JP, Clancy RM. Neonatal lupus: review of proposed pathogenesis and clinical data from the US-based Research Registry for Neonatal Lupus. *Autoimmunity* 2003;36:41–50.
 78. Zulian F, Pluchinotta F, Martini G, et al. Severe clinical course of systemic lupus erythematosus in the first year of life. *Lupus* 2008;17:780–6.
 79. Gomez-Moyano E, Vera-Casano A, Moreno-Perez D, et al. Lupus erythematosus-like lesions by voriconazole in an infant with chronic granulomatous disease. *Pediatr Dermatol* 2010;27(1):105–6.
 80. Sampaio MC, de Oliveira ZN, Machado MC, et al. Discoid lupus erythematosus in children – a retrospective study of 34 patients. *Pediatr Dermatol* 2008;25(2):163–7.
 81. Badri T, Khaddar RK, Bouraoui S, et al. Discoid lupus erythematosus in an infant. *Dermatol Online J* 2005;11(3):38.
 82. Hayakawa J, Migita M, Ueda T, et al. Infantile case of early manifestation of SLE-like symptoms in complete C1q deficiency. *J Nippon Med Sch* 2011;78:322–8.
 83. Rice G, Newman WG, Dean J, et al. Heterozygous mutations in TREX1 cause familial chilblain lupus and dominant Aicardi-Goutieres syndrome. *Am J Hum Genet* 2007;80:811–15.
 84. Ravenscroft JC, Suri M, Rice GI, et al. Autosomal dominant inheritance of a heterozygous mutation in SAMHD1 causing familial chilblain lupus. *Am J Med Genet A* 2011;155A:235–7.
 85. Zulian F, Vallongo C, de Oliveira SK, et al. Congenital localized scleroderma. *J Pediatr* 2006;149:248–51.
 86. Carder KR. Hypersensitivity reactions in neonates and infants. *Dermatol Ther* 2005;18(2):160–75.
 87. Wintroub BU, Stern R. Cutaneous drug reactions: pathogenesis and clinical classification. *J Am Acad Dermatol* 1985;13(2 Pt 1):167–79.
 88. Knowles S, Shapiro L, Shear NH. Serious dermatologic reactions in children. *Curr Opin Pediatr* 1997;9(4):388–95.
 89. Kramer MS, Hutchinson TA, Flegel KM, et al. Adverse drug reactions in general pediatric outpatients. *J Pediatr* 1985;106(2):305–10.
 90. Sharma VK, Dhar S. Clinical pattern of cutaneous drug eruption among children and adolescents in north India. *Pediatr Dermatol* 1995;12(2):178–83.
 91. Shin HT, Chang MW. Drug eruptions in children. *Curr Probl Pediatr* 2001;31(7):207–34.
 92. Stur K, Karlhofer FM, Stingl G. Soluble FAS ligand: a discriminating feature between drug-induced skin eruptions and viral exanthemas. *J Invest Dermatol* 2007;127(4):802–7.
 93. Chovel-Sella A, Ben Tov A, Lahav E, et al. Incidence of rash after amoxicillin treatment in children with infectious mononucleosis. *Pediatrics* 2013;131(5):e1424–7.
 94. Jappe U. Amoxicillin-induced exanthema in patients with infectious mononucleosis: allergy or transient immunostimulation? *Allergy* 2007;62(12):1474–5.
 95. Schaad UB, McCracken GH Jr, Nelson JD. Clinical pharmacology and efficacy of vancomycin in pediatric patients. *J Pediatr* 1980;96(1):119–26.
 96. Lacouture PG, Epstein MF, Mitchell AA. Vancomycin-associated shock and rash in newborn infants. *J Pediatr* 1987;111(4):615–16.
 97. Salomon D, Saurat JH. Erythema multiforme major in a 2-month-old child with human immunodeficiency virus (HIV) infection. *Br J Dermatol* 1990;123(6):797–800.
 98. Prose NS. Cutaneous manifestations of pediatric HIV infection. *Pediatr Dermatol* 1992;9(4):326–8.
 99. Chanock SJ, Luginbuhl LM, McIntosh K, et al. Life-threatening reaction to trimethoprim/sulfamethoxazole in pediatric human immunodeficiency virus infection. *Pediatrics* 1994;93(3):519–21.
 100. Cohen HA, Cohen Z, Frydman M. Fixed drug eruption of the scrotum due to hydroxyzine hydrochloride (Atarax). *Cutis* 1996;57(6):431–2.
 101. Dogra S, Handa S. Bullous necrotizing fixed drug eruption in an infant. *Pediatr Dermatol* 2004;21(3):281–2.
 102. Bel S, Bartralot R, Garcia D, et al. Vegetant bromoderma in an infant. *Pediatr Dermatol* 2001;18(4):336–8.
 103. Nabatame S, Saito Y, Sakuma H, et al. Bromoderma in a patient with migrating partial seizures in infancy. *Epilepsy Res* 2010;91(2–3):283–8.
 104. Torrello A, Madero L, Mediero IG, et al. A cutaneous eruption from G-CSF in a healthy donor. *Pediatr Dermatol* 2000;17(3):205–7.
 105. Buyukgebiz B, Arslan N, Ozturk Y, et al. Drug reaction to ursodeoxycholic acid: lichenoid drug eruption in an infant using ursodeoxycholic acid for neonatal hepatitis. *J Pediatr Gastroenterol Nutr* 2002;35(3):384–6.
 106. Menter MA. Hypertrichosis lanuginosa and a lichenoid eruption due to diazoxide therapy. *Proc R Soc Med* 1973;66(4):326–7.
 107. King BA, Geelhoed GC. Adverse skin and joint reactions associated with oral antibiotics in children: the role of cefaclor in serum sickness-like reactions. *J Paediatr Child Health* 2003;39(9):677–81.
 108. Vial T, Pont J, Pham E, et al. Cefaclor-associated serum sickness-like disease: eight cases and review of the literature. *Ann Pharmacother* 1992;26(7–8):910–14.
 109. Hebert AA, Sigman ES, Levy ML. Serum sickness-like reactions from cefaclor in children. *J Am Acad Dermatol* 1991;25(5 Pt 1):805–8.
 110. Meadows KP, Egan CA, Vanderhooft S. Acute generalized exanthematous pustulosis (AGEP), an uncommon condition in children: case report and review of the literature. *Pediatr Dermatol* 2000;17(5):399–402.
 111. Ersoy S, Paller AS, Mancini AJ. Acute generalized exanthematous pustulosis in children. *Arch Dermatol* 2004;140(9):1172–3.
 112. Roujeau JC, Bioulac-Sage P, Bourseau C, et al. Acute generalized exanthematous pustulosis. Analysis of 63 cases. *Arch Dermatol* 1991;127(9):1333–8.
 113. Carroll MC, Yueng-Yue KA, Esterly NB, et al. Drug-induced hypersensitivity syndrome in pediatric patients. *Pediatrics* 2001;108(2):485–92.
 114. Bessmertny O, Hatton RC, Gonzalez-Peralta RP. Antiepileptic hypersensitivity syndrome in children. *Ann Pharmacother* 2001;35(5):533–8.
 115. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part I. Clinical perspectives. *J Am Acad Dermatol* 2013;68(5):693.e1–e14.
 116. Yigit S, Korkmaz A, Sekerel B. Drug-induced hypersensitivity syndrome in a premature infant. *Pediatr Dermatol* 2005;22(1):71–4.
 117. Chen CJ, Huang YC, Wang CY, Lin TY. Fatal anticonvulsant hypersensitivity syndrome in an infant. *Eur J Pediatr* 2003;162(12):893–4.
 118. Kitcharoensakkul M, Ree N, Bloomberg GR, et al. Vancomycin-induced DRESS with evidence of T-cell activation in a 22-month-old patient. *Ann Allergy Asthma Immunol* 2012;109(4):280–1.
 119. Walsh S, Diaz-Cano S, Higgins E, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): Is cutaneous phenotype a prognostic marker for outcome? A review of

- clinicopathological features of 27 cases. *Br J Dermatol* 2013;168(2):391–401.
120. Shear NH, Spielberg SP. Anticonvulsant hypersensitivity syndrome. In vitro assessment of risk. *J Clin Invest* 1988;82(6):1826–32.
121. Rzyan B, Correia O, Kelly JP, et al. Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. *Lancet* 1999;353(9171):2190–4.
122. Mantadakis E, Tsalkidis A, Paraskakis E, et al. Anticonvulsant hypersensitivity syndrome closely mimicking Kawasaki disease. *BMJ Case Rep* 2009; doi: 10.1136/bcr.10.2008.1076.
123. Newell BD, Moinfar M, Mancini AJ, et al. Retrospective analysis of 32 pediatric patients with anticonvulsant hypersensitivity syndrome (ACHSS). *Pediatr Dermatol* 2009;26(5):536–46.
124. Scheuerman O, Nofech-Moses Y, Rachmel A, et al. Successful treatment of antiepileptic drug hypersensitivity syndrome with intravenous immune globulin. *Pediatrics* 2001;107(1):E14.
125. Husain Z, Reddy BY, Schwartz RA. DRESS syndrome: Part II. Management and therapeutics. *J Am Acad Dermatol* 2013;68(5):709.e1–e9.
126. Auquier-Dunant A, Mockenhaupt M, Naldi L, et al. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens–Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch Dermatol* 2002;138(8):1019–24.
127. Bastuji-Garin S, Rzyan B, Stern RS, et al. Clinical classification of cases of toxic epidermal necrolysis, Stevens–Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993;129(1):92–6.
128. Wetter DA, Camilleri MJ. Clinical, etiologic, and histopathologic features of Stevens–Johnson syndrome during an 8-year period at Mayo Clinic. *Mayo Clin Proc* 2010;85(2):131–8.
129. Ravin KA, Rappaport LD, Zuckerbraun NS, et al. Mycoplasma pneumoniae and atypical Stevens–Johnson syndrome: a case series. *Pediatrics* 2007;119(4):e1002–5.
130. Levy M, Shear NH. Mycoplasma pneumoniae infections and Stevens–Johnson syndrome. Report of eight cases and review of the literature. *Clin Pediatr (Phila)* 1991;30(1):42–9.
131. Pereira FA, Mudgil AV, Rosmarin DM. Toxic epidermal necrolysis. *J Am Acad Dermatol* 2007;56(2):181–200.
132. Mockenhaupt M, Viboud C, Dunant A, et al. Stevens–Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR Study. *J Invest Dermatol* 2008;128(1):35–44.
133. Levi N, Bastuji-Garin S, Mockenhaupt M, et al. Medications as risk factors of Stevens–Johnson syndrome and toxic epidermal necrolysis in children: a pooled analysis. *Pediatrics* 2009;123(2):e297–e304.
134. Lohmeier K, Megahed M, Schulte KW, et al. Toxic epidermal necrolysis in a premature infant of 27 weeks' gestational age. *Br J Dermatol* 2005;152(1):150–1.
135. Forman R, Koren G, Shear NH. Erythema multiforme, Stevens–Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years' experience. *Drug Saf* 2002;25(13):965–72.
136. Assier H, Bastuji-Garin S, Revuz J, et al. Erythema multiforme with mucous membrane involvement and Stevens–Johnson syndrome are clinically different disorders with distinct causes. *Arch Dermatol* 1995;131(5):539–43.
137. Metry DW, Jung P, Levy ML. Use of intravenous immunoglobulin in children with Stevens–Johnson syndrome and toxic epidermal necrolysis: seven cases and review of the literature. *Pediatrics* 2003;112(6 Pt 1):1430–6.
138. Mockenhaupt M. The current understanding of Stevens–Johnson syndrome and toxic epidermal necrolysis. *Expert Rev Clin Immunol* 2011;7(6):803–13; quiz 14–15.
139. Finkelstein Y, Soon GS, Acuna P, et al. Recurrence and outcomes of Stevens–Johnson syndrome and toxic epidermal necrolysis in children. *Pediatrics* 2011;128(4):723–8.
140. Schneck J, Fagot JP, Sekula P, et al. Effects of treatments on the mortality of Stevens–Johnson syndrome and toxic epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. *J Am Acad Dermatol* 2008;58(1):33–40.
141. Chung WH, Hung SI, Chen YT. Human leukocyte antigens and drug hypersensitivity. *Curr Opin Allergy Clin Immunol* 2007;7(4):317–23.
142. Brice SL, Huff JC, Weston WL. Erythema multiforme minor in children. *Pediatrician* 1991;18(3):188–94.
143. Dikland WJ, Oranje AP, Stolz E, van Joost T. Erythema multiforme in childhood and early infancy. *Pediatr Dermatol* 1986;3(2):135–9.
144. Hurwitz S. Erythema multiforme: a review of its characteristics, diagnostic criteria, and management. *Pediatr Rev* 1990;11(7):217–22.
145. Roujeau JC. Stevens–Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. *J Dermatol* 1997;24(11):726–9.
146. Cho YJ, Huh SY, Hong JS, et al. Neonatal erythema multiforme: a case report. *Ann Dermatol* 2011;23(3):382–5.
147. Ang-Tiu CU, Nicolas ME. Erythema multiforme in a 25-day old neonate. *Pediatr Dermatol* 2012; Sep 20, doi: 10.1111/j.1525-4702.2012.01873.x. [Epub ahead of print].
148. Ashkenazi S, Metzker A, Rachmel A, et al. Erythema multiforme as a single manifestation of cow's milk intolerance. *Acta Paediatr* 1992;81(9):729–30.
149. Johnston GA, Ghura HS, Carter E, et al. Neonatal erythema multiforme major. *Clin Exp Dermatol* 2002;27(8):661–4.
150. Torrello A, Moreno M, de Prada I, et al. Erythema multiforme in a neonate. *J Am Acad Dermatol* 2003;48(5 Suppl):S78–9.
151. Nanda S, Pandhi D, Reddy BS. Erythema multiforme in a 9-day-old neonate. *Pediatr Dermatol* 2003;20(5):454–5.
152. Sakurai N. Erythema multiforme in children: unusual clinical features with seasonal occurrence. *J Dermatol* 1989;16(5):361–8.
153. Weston WL, Brice SL, Jester JD, et al. Herpes simplex virus in childhood erythema multiforme. *Pediatrics* 1992;89(1):32–4.
154. Frederiksen MS, Brenoe E, Trier J. Erythema multiforme minor following vaccination with paediatric vaccines. *Scand J Infect Dis* 2004;36(2):154–5.
155. Renfro L, Grant-Kels JM, Feder HM Jr, et al. Controversy: are systemic steroids indicated in the treatment of erythema multiforme? *Pediatr Dermatol* 1989;6(1):43–50.
156. Yeung AK, Goldman RD. Use of steroids for erythema multiforme in children. *Can Fam Physician* 2005;51:1481–3.
157. Tatnall FM, Schofield JK, Leigh IM. A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. *Br J Dermatol* 1995;132(2):267–70.
158. Tamayo-Sanchez L, Ruiz-Maldonado R, Laterza A. Acute annular urticaria in infants and children. *Pediatr Dermatol* 1997;14:231–4.
159. Haas N, Birkle-Berlinger W, Henz BM. Prognosis of acute urticaria in children. *Acta Dermatol Venereol* 2005;85:74–5.
160. Sackesen C, Sekerel BE, Orhan F, et al. The etiology of different forms of urticaria in childhood. *Pediatr Dermatol* 2004;21:102–8.
161. Mortureux P, Leaute-Labreze C, Legrain-Lifermann V, et al. Acute urticaria in infancy and early childhood: a prospective study. *Arch Dermatol* 1998;134:319–23.
162. Beltrani VS. Urticaria: reassessed. *Allergy Asthma Proc* 2004;25:143–9.
163. Ghosh S, Kanwar AJ, Kaur S. Urticaria in children. *Pediatr Dermatol* 1993;10:107–10.
164. Legrain V, Taieb A, Sage T, et al. Urticaria in infants: a study of forty patients. *Pediatr Dermatol* 1990;7:101–7.
165. Kauppinen K, Juntunen K, Lanki H. Urticaria in children. Retrospective evaluation and follow-up. *Allergy* 1984;39:469–72.
166. Carter EL, Garzon MC. Neonatal urticaria due to prostaglandin E1. *Pediatr Dermatol* 2000;17:58–61.
167. Borghesi A, Cipelletti P, Maragliano R, et al. Human herpesvirus-6 associated neonatal urticaria multiforme. *Arch Dis Child Fetal Neonatal Ed* 2012;98(5):F450.
168. Hamel-Teillac D. Les urticaires chroniques de l'enfant. *Ann Dermatol Venereol* 2003;130:1569–72.
169. Pite H, Wedi B, Borrego LM, et al. Management of childhood urticaria: current knowledge and practical recommendations. *Acta Derm Venereol* 2013;93(5):500–8.
170. Dice JP. Physical urticaria. *Immunol Allergy Clin North Am* 2004;24:225–46.
171. Shah KN, Honig PJ, Yan AC. 'Urticaria multiforme': a case series and review of acute annular urticarial hypersensitivity syndromes in children. *Pediatrics* 2007;119(5):e1177–83.
172. Ruiz-Maldonado R, Tamayo L, Ridaura C. Diffuse dermographic mastocytosis without visible skin lesions. *Int J Dermatol* 1975;14:126–8.
173. Estelle F, Simons R, Silas P, et al. Safety of cetirizine in infants 6 to 11 months of age: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2003;111:1244–8.
174. Hampel F, Ratner P, Haeusler JM. Safety and tolerability of levocetirizine dihydrochloride in infants and children with allergic rhinitis or chronic urticaria. *Allergy Asthma Proc* 2010;31:290–5.
175. Jedeke KB, Michels VV. Familial dermatographism. *Am J Med Genet* 1991;39:201–3.
176. Epstein PA, Kidd KK. Dermo-distortive urticaria: an autosomal dominant dermatologic disorder. *Am J Med Genet* 1981;9:307–15.
177. Patterson R, Mellies CJ, Blankenship ML, et al. Vibratory angioedema: a hereditary type of physical hypersensitivity. *J Allergy Clin Immunol* 1972;50:174–82.
178. Bonnetblanc JM, Andrieu-Pfah E, Meraud JP, et al. Familial aquagenic urticaria. *Dermatologia* 1979;158:468–70.

179. Bork K, Meng G, Staubach P, et al. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006;119:267.
180. Kastner DL, Aksentijevich I, Goldbach-Mansky R. Autoinflammatory disease reloaded: a clinical perspective. *Cell* 2010;140:784–90.
181. Savic S, Dickie LJ, Wittmann M, et al. Autoinflammatory syndromes and cellular responses to stress: pathophysiology, diagnosis and new treatment perspectives. *Best Pract Res Clin Rheumatol* 2012;26:505–33.
182. Goldbach-Mansky R, Kastner DL. Autoinflammation: the prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. *J Allergy Clin Immunol* 2009;124:1141–9.
183. Wanderer AA, Hoffman HM. The spectrum of acquired and familial cold-induced urticaria/urticaria-like syndromes. *Immunol Allergy Clin North Am* 2004;24:259–86.
184. Zip CM, Ross JB, Greaves MW, et al. Familial cold urticaria. *Clin Exp Dermatol* 1993;18:338–41.
185. Tindall JP, Beeker SK, Rosse WF. Familial cold urticaria. A generalized reaction involving leukocytosis. *Arch Intern Med* 1969;124:129–34.
186. Doeglas HM, Bleumink E. Familial cold urticaria. Clinical findings. *Arch Dermatol* 1974;110:382–8.
187. Ormerod AD, Smart L, Reid TM, et al. Familial cold urticaria. Investigation of a family and response to stanazolol. *Arch Dermatol* 1993;129:343–6.
188. Haas N, Kuster W, Zuberbier T, et al. Muckle-Wells syndrome: clinical and histological skin findings compatible with cold air urticaria in a large kindred. *Br J Dermatol* 2004;151:99–104.
189. Dode C, Le DN, Cuisset L, et al. New mutations of CIAS1 that are responsible for Muckle-Wells syndrome and familial cold urticaria: a novel mutation underlies both syndromes. *Am J Hum Genet* 2002;70:1498–506.
190. Pradaliere A, Cauvain A, Oukachbi Z. Inherited autoinflammatory recurrent fevers. *Allerg Immunol (Paris)* 2006;38:5–9.
191. Kildine C, Shinkai K, Bree A, et al. Neonatal-onset multisystem inflammatory disorder: the emerging role of pyrin genes in autoinflammatory diseases. *Arch Dermatol* 2005;141:248–53.
192. Hull KM, Shoham N, Chae JJ, et al. The expanding spectrum of systemic autoinflammatory disorders and their rheumatic manifestations. *Curr Opin Rheumatol* 2003;15:61–9.
193. Prieur AM. A recently recognised chronic inflammatory disease of early onset characterised by the triad of rash, central nervous system involvement and arthropathy. *Clin Exp Rheumatol* 2001;19:103–6.
194. Huttenlocher A, Frieden IJ, Emery H. Neonatal onset multisystem inflammatory disease. *J Rheumatol* 1995;22:1171–3.
195. Torbiak RP, Dent PB, Cockshott WP. NOMID – a neonatal syndrome of multisystem inflammation. *Skeletal Radiol* 1989;18:359–64.
196. Feldmann J, Prieur AM, Quartier P, et al. Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in CIAS1, a gene highly expressed in polymorphonuclear cells and chondrocytes. *Am J Hum Genet* 2002;71:198–203.
197. Neven B, Callebaut I, Prieur AM, et al. Molecular basis of the spectral expression of CIAS1 mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. *Blood* 2004;103:2809–15.
198. Glaser RL, Goldbach-Mansky R. The spectrum of monogenic autoinflammatory syndromes: understanding disease mechanisms and use of targeted therapies. *Curr Allergy Asthma Rep* 2008;8:288–98.
199. Miura M, Okabe T, Tsubata S, et al. Chronic infantile neurological cutaneous articular syndrome in a patient from Japan. *Eur J Pediatr* 1997;156:624–6.
200. Hassink SG, Goldsmith DP. Neonatal onset multisystem inflammatory disease. *Arthritis Rheum* 1983;26:668–73.
201. Kallinich T, Hoffman HM, Roth J, et al. The clinical course of a child with CINCA/NOMID syndrome improved during and after treatment with thalidomide. *Scand J Rheumatol* 2005;34:246–9.
202. Hawkins PN, Lachmann HJ, Aganna E, et al. Spectrum of clinical features in Muckle-Wells syndrome and response to anakinra. *Arthritis Rheum* 2004;50:607–12.
203. Boschan C, Witt O, Lohse P, et al. Neonatal-onset multisystem inflammatory disease (NOMID) due to a novel S331R mutation of the CIAS1 gene and response to interleukin-1 receptor antagonist treatment. *Am J Med Genet A* 2006;140:883–6.
204. Lovell DJ, Bowyer SL, Solinger AM. Interleukin-1 blockade by anakinra improves clinical symptoms in patients with neonatal-onset multisystem inflammatory disease. *Arthritis Rheum* 2005;52:1283–6.
205. Matsubayashi T, Sugiura H, Arai T, et al. Anakinra therapy for CINCA syndrome with a novel mutation in exon 4 of the CIAS1 gene. *Acta Paediatr* 2006;95:246–9.
206. Federico G, Rigante D, Pugliese AL, et al. Etanercept induces improvement of arthropathy in chronic infantile neurological cutaneous articular (CINCA) syndrome. *Scand J Rheumatol* 2003;32:312–14.
207. Koné-Paut I, Píram M. Targeting interleukin-1 β in CAPS (cryopyrin-associated periodic) syndromes: What did we learn? *Autoimmun Rev* 2012;12:77–80.
208. Aksentijevich I, Masters SL, Ferguson PJ, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *N Engl J Med* 2009;360:2426–37.
209. Minkis K, Aksentijevich I, Goldbach-Mansky R, et al. Interleukin 1 receptor antagonist deficiency presenting as infantile pustulosis mimicking infantile pustular psoriasis. *Arch Dermatol* 2012;148:747–52.
210. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med* 2011;365:620–8.
211. Torrello A, Patel S, Colmenero I, et al. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. *J Am Acad Dermatol* 2010;62:489–95.
212. Liu Y, Ramot Y, Torrello A, et al. Mutations in proteasome subunit β type 8 cause chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature with evidence of genetic and phenotypic heterogeneity. *Arthritis Rheum* 2012;64:895–907.
213. Gilliam AE, Bruckner AL, Howard RM, et al. Bullous 'cellulitis' with eosinophilia: case report and review of Wells' syndrome in childhood. *Pediatrics* 2005;116(1):e149–55.
214. Kuwahara RT, Randall MB, Eisner MG. Eosinophilic cellulitis in a newborn. *Pediatr Dermatol* 2001;18(1):89–90.
215. Kamani N, Lipsitz PJ. Eosinophilic cellulitis in a family. *Pediatr Dermatol* 1987;4(3):220–4.
216. Garty BZ, Feinmesser M, David M, et al. Congenital Wells syndrome. *Pediatr Dermatol* 1997;14(4):312–15.
217. Caputo R, Marzano AV, Vezzoli P, et al. Wells syndrome in adults and children: a report of 19 cases. *Arch Dermatol* 2006;142(9):1157–61.
218. Cherng E, McClung AA, Rosenthal HM, et al. Wells' syndrome associated with parvovirus in a 5-year old boy. *Pediatr Dermatol* 2012;29(6):762–4.
219. Hamamoto Y, Ichimiya M, Yoshikawa Y, et al. Eosinophilic cellulitis associated with molluscum contagiosum. *Br J Dermatol* 2004;151(6):1279–81.
220. Koh KJ, Warren L, Moore L, et al. Wells' syndrome following thiomersal-containing vaccinations. *Australas J Dermatol* 2003;44(3):199–202.
221. Tsuda S, Tanaka K, Miyasato M, et al. Eosinophilic cellulitis (Wells' syndrome) associated with ascariasis. *Acta Derm Venereol* 1994;74(4):292–4.
222. Stavropoulos PG, Kostakis PG, Panagiotopoulos AK, et al. Molluscum contagiosum and cryosurgery: triggering factors for Wells' syndrome? *Acta Derm Venereol* 2003;83(5):380–1.
223. Moon SH, Shin MK. Bullous eosinophilic cellulitis in a child treated with dapsone. *Pediatr Dermatol* 2013;30(4):e46–7.
224. Shams M, Hudgens J, Leshner JL Jr, et al. Wells' syndrome presenting as a noninfectious bullous cellulitis in a child. *Pediatr Dermatol* 2012;29(2):224–6.
225. Van der Straaten S, Wojciechowski M, Salgado R, et al. Eosinophilic cellulitis or Wells' syndrome in a 6-year-old child. *Eur J Pediatr* 2006;165(3):197–8.
226. Consigny S, Courville P, Young P, et al. [Histological and clinical forms of the eosinophilic cellulitis]. *Ann Dermatol Venereol* 2001;128(3 Pt 1):213–16.
227. French LE, Shapiro M, Junkins-Hopkins JM, et al. Eosinophilic fasciitis and eosinophilic cellulitis in a patient with abnormal circulating clonal T cells: increased production of interleukin 5 and inhibition by interferon alfa. *J Am Acad Dermatol* 2003;49(6):1170–4.
228. Fujii K, Tanabe H, Kanno Y, et al. Eosinophilic cellulitis as a cutaneous manifestation of idiopathic hypereosinophilic syndrome. *J Am Acad Dermatol* 2003;49(6):1174–7.
229. Fujimoto N, Wakabayashi M, Kato T, et al. Wells syndrome associated with Churg-Strauss syndrome. *Clin Exp Dermatol* 2011;36(1):46–8.
230. Rongioletti F, Fausti V, Kempf W, et al. Eosinophilic annular erythema: an expression of the clinical and pathological polymorphism of Wells syndrome. *J Am Acad Dermatol* 2011;65(4):e135–7.
231. El-Khalawany M, Al-Mutairi N, Sultan M, et al. Eosinophilic annular erythema is a peculiar subtype in the spectrum of Wells syndrome: a multicentre long-term follow-up study. *J Eur Acad Dermatol Venereol* 2012;27(8):973–9.
232. Peterson AO Jr, Jarratt M. Annular erythema of infancy. *Arch Dermatol* 1981;117(3):145–8.
233. Helm TN, Bass J, Chang IW, et al. Persistent annular erythema of infancy. *Pediatr Dermatol* 1993;10(1):46–8.

234. Cohen PR, Kurzrock R. Sweet's syndrome revisited: a review of disease concepts. *Int J Dermatol* 2003;42:761–78.
235. Callen JP. Neutrophilic dermatoses. *Dermatol Clin* 2002;20:409–19.
236. Fitzgerald RL, McBurney EI, Nesbitt LT Jr. Sweet's syndrome. *Int J Dermatol* 1996;35:9–15.
237. von den DP. Sweet's syndrome (acute febrile neutrophilic dermatosis). *J Am Acad Dermatol* 1994;31:535–56.
238. Kemmett D, Hunter JA. Sweet's syndrome: a clinicopathologic review of twenty-nine cases. *J Am Acad Dermatol* 1990;23:503–7.
239. Dunn TR, Saperstein HW, Biederman A, et al. Sweet syndrome in a neonate with aseptic meningitis. *Pediatr Dermatol* 1992;9:288–92.
240. Hassouna L, Nabulsi-Khalil M, Mroueh SM, et al. Multiple erythematous tender papules and nodules in an 11-month-old boy. Sweet syndrome (SS) (acute febrile neutrophilic dermatosis). *Arch Dermatol* 1996;132:1507, 1510.
241. Levin DL, Esterly NB, Herman JJ, et al. The Sweet syndrome in children. *J Pediatr* 1981;99:73–8.
242. Prasad PV, Ambujam S, Priya K, et al. Sweet's syndrome in an infant – report of a rare case. *Int J Dermatol* 2002;41:928–30.
243. Sedel D, Huguet P, Lebbe C, et al. Sweet syndrome as the presenting manifestation of chronic granulomatous disease in an infant. *Pediatr Dermatol* 1994;11:237–40.
244. Brady RC, Morris J, Connelly BL, et al. Sweet's syndrome as an initial manifestation of pediatric human immunodeficiency virus infection. *Pediatrics* 1999;104:1142–4.
245. Collins P, Rogers S, Keenan P, et al. Acute febrile neutrophilic dermatosis in childhood (Sweet's syndrome). *Br J Dermatol* 1991;124:203–6.
246. Haliasos E, Soder B, Rubenstein DS, et al. Pediatric Sweet syndrome and immunodeficiency successfully treated with intravenous immunoglobulin. *Pediatr Dermatol* 2005;22:530–5.
247. Hazen PG, Kark EC, Davis BR, et al. Acute febrile neutrophilic dermatosis in children. Report of two cases in male infants. *Arch Dermatol* 1983;119:998–1002.
248. Itami S, Nishioka K. Sweet's syndrome in infancy. *Br J Dermatol* 1980;103:449–51.
249. Lipp KE, Shenefelt PD, Nelson RP Jr, et al. Persistent Sweet's syndrome occurring in a child with a primary immunodeficiency. *J Am Acad Dermatol* 1999;40:838–41.
250. Parsapour K, Reep MD, Gohar K, et al. Familial Sweet's syndrome in 2 brothers, both seen in the first 2 weeks of life. *J Am Acad Dermatol* 2003;49:132–8.
251. Saxe N, Gordon W. Acute febrile neutrophilic dermatosis (Sweet's syndrome). Four case reports. *S Afr Med J* 1978;53:253–6.
252. Tuerlinckx D, Bodart E, Despontin K, et al. Sweet's syndrome with arthritis in an 8-month-old boy. *J Rheumatol* 1999;26:440–2.
253. Uihlein LC, Brandling-Bennett HA, Lio PA, et al. Sweet syndrome in children. *Pediatr Dermatol* 2012;29:38–44.
254. Hwang ST, Williams ML, McCalmont TH, et al. Sweet's syndrome leading to acquired cutis laxa (Marshall's syndrome) in an infant with alpha 1-antitrypsin deficiency. *Arch Dermatol* 1995;131:1175–7.
255. Nobeyama Y, Kamide R. Sweet's syndrome with neurologic manifestation: case report and literature review. *Int J Dermatol* 2003;42:438–43.
256. Gray PE, Bock V, Ziegler DS, et al. Neonatal Sweet syndrome: a potential marker of serious systemic illness. *Pediatrics* 2012;129:e1353–9.
257. Cohen PR, Kurzrock R. Sweet's syndrome and cancer. *Clin Dermatol* 1993;11:149–57.
258. Walker DC, Cohen PR. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. *J Am Acad Dermatol* 1996;34:918–23.
259. Govindarajan G, Bashir Q, Kuppuswamy S, et al. Sweet syndrome associated with furosemide. *South Med J* 2005;98:570–2.
260. Khan DB, Jappe U. Drug-induced Sweet's syndrome in acne caused by different tetracyclines: case report and review of the literature. *Br J Dermatol* 2002;147:558–62.
261. Jain KK. Sweet's syndrome associated with granulocyte colony-stimulating factor. *Cutis* 1996;57:107–10.
262. Jovanovic M, Poljacki M, Vujanovic L, et al. Acute febrile neutrophilic dermatosis (Sweet's syndrome) after influenza vaccination. *J Am Acad Dermatol* 2005;52:367–9.
263. Cohen PR, Kurzrock R. Sweet's syndrome: a review of current treatment options. *Am J Clin Dermatol* 2002;3:117–31.
264. Myatt AE, Baker DJ, Byfield DM. Sweet's syndrome: a report on the use of potassium iodide. *Clin Exp Dermatol* 1987;12:345–9.
265. Suehisa S, Tagami H, Inoue F, et al. Colchicine in the treatment of acute febrile neutrophilic dermatosis (Sweet's syndrome). *Br J Dermatol* 1983;108:99–101.
266. Aram H. Acute febrile neutrophilic dermatosis (Sweet's syndrome). Response to dapsone. *Arch Dermatol* 1984;120:245–7.
267. Scuccimarrì R. Kawasaki disease. *Pediatr Clin North Am* 2012;59(2):425–45.
268. Yim D, Curtis N, Cheung M, et al. Update on Kawasaki disease: epidemiology, aetiology and pathogenesis. *J Paediatr Child Health* 2013;49(9):704–8.
269. Yim D, Curtis N, Cheung M, Burgner D. An update on Kawasaki disease II: clinical features, diagnosis, treatment and outcomes. *J Paediatr Child Health* 2013;49(8):614–23.
270. Levin M, Tizard EJ, Dillon MJ. Kawasaki disease: recent advances. *Arch Dis Child* 1991;66:1369–72.
271. Rosenfeld EA, Corydon KE, Shulman ST. Kawasaki disease in infants less than one year of age. *J Pediatr* 1995;126:524–9.
272. Burns JC, Wiggins JW Jr, Toews WH, et al. Clinical spectrum of Kawasaki disease in infants younger than 6 months of age. *J Pediatr* 1986;109:759–63.
273. Stanley TV, Grimwood K. Classical Kawasaki disease in a neonate. *Arch Dis Child Fetal Neonatal Ed* 2002;86:F135–6.
274. Krapf R, Zimmermann A, Stocker F. Lethal vasculitis of coronary arteries in a neonate and two infants: possible neonatal variant of the MLNS/IPN complex? *Helv Paediatr Acta* 1981;36:589–98.
275. Bolz D, Arbenz U, Fanconi S, et al. Myocarditis and coronary dilatation in the 1st week of life: neonatal incomplete Kawasaki disease? *Eur J Pediatr* 1998;157:589–91.
276. Burgner D, Harnden A. Kawasaki disease: what is the epidemiology telling us about the etiology? *Int J Infect Dis* 2005;9:185–94.
277. Fujita Y, Nakamura Y, Sakata K, et al. Kawasaki disease in families. *Pediatrics* 1989;84:666–9.
278. Newburger JW, Fulton DR. Kawasaki disease. *Curr Opin Pediatr* 2004;16:508–14.
279. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004;114:1708–33.
280. Friter BS, Lucky AW. The perineal eruption of Kawasaki syndrome. *Arch Dermatol* 1988;124:1805–10.
281. Tomita S, Chung K, Mas M, et al. Peripheral gangrene associated with Kawasaki disease. *Clin Infect Dis* 1992;14:121–6.
282. Sinha R, Balakumar T. BCG reactivation: a useful diagnostic tool even for incomplete Kawasaki disease. *Arch Dis Child* 2005;90:891.
283. Takeuchi M, Oda Y, Suzuki I. Maculopapular rash in the convalescent phase of Kawasaki disease: case series and literature review. *Eur J Pediatr* 2012; PMID: 23192460.
284. Eberhard BA, Sundel RP, Newburger JW, et al. Psoriatic eruption in Kawasaki disease. *J Pediatr* 2000;137:578–80.
285. Zvulunov A, Greenberg D, Cagnano E, et al. Development of psoriatic lesions during acute and convalescent phases of Kawasaki disease. *J Paediatr Child Health* 2003;39:229–31.
286. Garty B, Mosseri R, Finkelstein Y. Guttae psoriasis following Kawasaki disease. *Pediatr Dermatol* 2001;18:507–8.
287. Tsai HJ, Wu WM, Chang YC, et al. Annular pustules in Kawasaki disease: a further case indicating the association with psoriasis? *Cutis* 2003;72:354–6.
288. Falcini F. Kawasaki disease. *Curr Opin Rheumatol* 2006;18:33–8.
289. Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;87:1776–80.
290. Witt MT, Minich LL, Bohnsack JF, et al. Kawasaki disease: more patients are being diagnosed who do not meet American Heart Association criteria. *Pediatrics* 1999;104:e10.
291. Alexandra FF. Inflammatory pulmonary nodules in Kawasaki disease. *Pediatr Pulmonol* 2003;36:102–6.
292. Palmer AL, Walker T, Smith JC. Acute respiratory distress syndrome in a child with Kawasaki disease. *South Med J* 2005;98:1031–3.
293. Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndrome after Kawasaki disease. *Pediatr Infect Dis J* 2003;22:663–6.
294. Knott PD, Orloff LA, Harris JP, et al. Sensorineural hearing loss and Kawasaki disease: A prospective study. *Am J Otolaryngol* 2001;22:343–8.
295. Yeung RS. Pathogenesis and treatment of Kawasaki's disease. *Curr Opin Rheumatol* 2005;17:617–23.
296. Wang CL, Wu YT, Liu CA, et al. Kawasaki disease: infection, immunity and genetics. *Pediatr Infect Dis J* 2005;24:998–1004.
297. Burns JC, Shimizu C, Gonzalez E, et al. Genetic variations in the receptor-ligand pair CCR5 and CCL3L1 are important determinants of susceptibility to Kawasaki disease. *J Infect Dis* 2005;192:344–9.
298. Hewitt M, Smith LJ, Joffe HS, et al. Kawasaki disease in siblings. *Arch Dis Child* 1989;64:398–9.
299. Dergun M, Kao A, Hauger SB, et al. Familial occurrence of Kawasaki syndrome in North America. *Arch Pediatr Adolesc Med* 2005;159:876–81.

300. Uehara R, Yashiro M, Nakamura Y, et al. Clinical features of patients with Kawasaki disease whose parents had the same disease. *Arch Pediatr Adolesc Med* 2004;158:1166–9.
301. Newburger JW, Burns JC, Beiser AS, et al. Altered lipid profile after Kawasaki syndrome. *Circulation* 1991;84:625–31.
302. Kawasaki T, Kosaki F, Okawa S, et al. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. *Pediatrics* 1974;54:271–6.
303. Burns JC, Glode MP. Kawasaki syndrome. *Lancet* 2004;364:533–44.
304. Simonini G, Rose CD, Vierucci A, et al. Diagnosing Kawasaki syndrome: the need for a new clinical tool. *Rheumatology (Oxford)* 2005;44:959–61.
305. Falcini F, Ozen S, Magni-Manzoni S, et al. Discrimination between incomplete and atypical Kawasaki syndrome versus other febrile diseases in childhood: results from an international registry-based study. *Clin Exp Rheumatol* 2012;30:799–804.
306. Ling XB, Kanegaye JT, Ji J, et al. Point-of-care differentiation of Kawasaki disease from other febrile illnesses. *J Pediatr* 2013;162(1):183–8.
307. Singh-Grewal D, Wong M, Isaacs D. Diagnosis, treatment and outcome of Kawasaki disease in an Australian tertiary setting: a review of three years experience. *J Paediatr Child Health* 2005;41:495–9.
308. Tsuda E, Kitamura S. National survey of coronary artery bypass grafting for coronary stenosis caused by Kawasaki disease in Japan. *Circulation* 2004;110:II61–6.
309. Nakamura Y, Aso E, Yashiro M, et al. Mortality among persons with a history of Kawasaki disease in Japan: can paediatricians safely discontinue follow-up of children with a history of the disease but without cardiac sequelae? *Acta Paediatr* 2005;94:429–34.
310. Nakamura Y, Yanagawa H, Harada K, et al. Mortality among persons with a history of Kawasaki disease in Japan: the fifth look. *Arch Pediatr Adolesc Med* 2002;156:162–5.
311. Levy DM, Silverman ED, Massicotte MP, et al. Longterm outcomes in patients with giant aneurysms secondary to Kawasaki disease. *J Rheumatol* 2005;32:928–34.
312. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation* 1996;94:1379–85.
313. Dajani AS, Taubert KA, Takahashi M, et al. Guidelines for long-term management of patients with Kawasaki disease. Report from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1994;89:916–22.
314. Nakamura Y, Yanagawa H, Harada K, et al. Mortality among persons with a history of Kawasaki disease in Japan: existence of cardiac sequelae elevated the mortality. *J Epidemiol* 2000;10:372–5.
315. de ZA, Colan SD, Gauvreau K, Baker AL, et al. Coronary artery dimensions may be misclassified as normal in Kawasaki disease. *J Pediatr* 1998;133:254–8.
316. Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose. *J Pediatr* 1997;131:888–93.
317. Durongpisitkul K, Gururaj VJ, Park JM, et al. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. *Pediatrics* 1995;96:1057–61.
318. Newburger JW, Takahashi M, Burns JC, et al. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med* 1986;315:341–7.
319. Furusho K, Kamiya T, Nakano H, et al. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet* 1984;2:1055–8.
320. Fong NC, Hui YW, Li CK, et al. Evaluation of the efficacy of treatment of Kawasaki disease before day 5 of illness. *Pediatr Cardiol* 2004;25:31–4.
321. Muta H, Ishii M, Egami K, et al. Early intravenous gamma-globulin treatment for Kawasaki disease: The nationwide surveys in Japan. *J Pediatr* 2004;144:496–9.
322. Marasini M, Pongiglione G, Gazzolo D, et al. Late intravenous gamma globulin treatment in infants and children with Kawasaki disease and coronary artery abnormalities. *Am J Cardiol* 1991;68:796–7.
323. Brogan PA, Bose A, Burgner D, et al. Kawasaki disease: an evidence based approach to diagnosis, treatment, and proposals for future research. *Arch Dis Child* 2002;86:286–90.
324. Sundel RP, Baker AL, Fulton DR, et al. Corticosteroids in the initial treatment of Kawasaki disease: Report of a randomized trial. *J Pediatr* 2003;142:611–16.
325. Okada Y, Shinohara M, Kobayashi T, et al. Effect of corticosteroids in addition to intravenous gamma globulin therapy on serum cytokine levels in the acute phase of Kawasaki disease in children. *J Pediatr* 2003;143:363–7.
326. Kobayashi T, Saji T, Otani T, et al. for the RAISE Study Group. Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease (RAISE study): a randomised, open-label, blinded-endpoints trial. *Lancet* 2012;379:1613–20.
327. Chen S, Dong Y, Yin Y, et al. Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis. *Heart* 2013;99(2):76–82.
328. Teraguchi M, Ogino H, Yoshimura K, et al. Steroid pulse therapy for children with intravenous immunoglobulin therapy-resistant Kawasaki disease: a prospective study. *Pediatr Cardiol* 2013;34(4):959–63.
329. Burns JC, Mason WH, Hauger SB, et al. Infliximab treatment for refractory Kawasaki syndrome. *J Pediatr* 2005;146:662–7.
330. Tacke CE, Burgner D, Kuipers IM, et al. Management of acute and refractory Kawasaki disease. *Expert Rev Anti Infect Ther* 2012;10:1203–15.
331. Baselga E, Drolet BA, Esterly NB. Purpura in infants and children. *J Am Acad Dermatol* 1997;37(5 Pt 1):673–705; quiz 6–7.
332. Caksen H, Odabas D, Kosem M, et al. Report of eight infants with acute infantile hemorrhagic edema and review of the literature. *J Dermatol* 2002;29(5):290–5.
333. Cox NH. Seidlmayer's syndrome: postinfectious coccidial purpura of early childhood. *J Am Acad Dermatol* 1992;26(2 Pt 1):275.
334. Cunningham BB, Caro WA, Eramo LR. Neonatal acute hemorrhagic edema of childhood: case report and review of the English-language literature. *Pediatr Dermatol* 1996;13(1):39–44.
335. Cunningham BB, Eramo L, Caro W. Acute hemorrhagic edema of childhood present at birth. *Pediatr Dermatol* 1999;16(1):68.
336. Gonggryp LA, Todd G. Acute hemorrhagic edema of childhood (AHE). *Pediatr Dermatol* 1998;15(2):91–6.
337. Ince E, Mumcu Y, Suskan E, et al. Infantile acute hemorrhagic edema: a variant of leukocytoclastic vasculitis. *Pediatr Dermatol* 1995;12(3):224–7.
338. Legrain V, Lejeune S, Taieb A, et al. Infantile acute hemorrhagic edema of the skin: study of ten cases. *J Am Acad Dermatol* 1991;24(1):17–22.
339. Larregue M, Lorette G, Prigent F, et al. [Acute haemorrhagic edema of the skin of the newborn with lethal intestinal complication] (author's transl). *Ann Dermatol Venereol* 1980;107(10):901–5.
340. Saraclar Y, Tinaztepe K, Adalioglu G, et al. Acute hemorrhagic edema of infancy (AHEI) – a variant of Henoch–Schönlein purpura or a distinct clinical entity? *J Allergy Clin Immunol* 1990;86(4 Pt 1):473–83.
341. Dubin BA, Bronson DM, Eng AM. Acute hemorrhagic edema of childhood: an unusual variant of leukocytoclastic vasculitis. *J Am Acad Dermatol* 1990;23(2 Pt 2):347–50.
342. Obeid M, Haley J, Crews J, et al. Acute hemorrhagic edema of infancy with abdominal pain and elevated transaminases. *Pediatr Dermatol* 2008;25(6):640–1.
343. Yu JE, Mancini AJ, Miller ML. Intussusception in an infant with acute hemorrhagic edema of infancy. *Pediatr Dermatol* 2007;24(1):61–4.
344. Amitai Y, Gillis D, Wasserman D, Kochman RH. Henoch–Schönlein purpura in infants. *Pediatrics* 1993;92(6):865–7.
345. Lambert D, Laurent R, Bouilly D, et al. [Haemorrhagic oedema acute in neonatal skin. Immunological and ultrastructural examination] (author's transl). *Ann Dermatol Venereol* 1979;106(12):975–87.
346. Saraclar Y, Tinaztepe K. Infantile acute hemorrhagic edema of the skin. *J Am Acad Dermatol* 1992;26(2 Pt 1):275–6.
347. Chandrakasan S, Singh S, Dogra S, et al. Wiskott–Aldrich syndrome presenting with early onset recurrent acute hemorrhagic edema and hyperostosis. *Pediatr Blood Cancer* 2011;56(7):1130–2.
348. Gedalia A. Henoch–Schönlein purpura. *Curr Rheumatol Rep* 2004;6(3):195–202.
349. Trapani S, Micheli A, Grisolia F, et al. Henoch–Schönlein purpura in childhood: epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. *Semin Arthritis Rheum* 2005;35(3):143–53.
350. Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PRIS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006;65(7):936–41.
351. Chang WL, Yang YH, Lin YT, et al. Gastrointestinal manifestations in Henoch–Schönlein purpura: a review of 261 patients. *Acta Paediatr* 2004;93(11):1427–31.
352. Sano H, Izumida M, Shimizu H, et al. Risk factors of renal involvement and significant proteinuria in Henoch–Schönlein purpura. *Eur J Pediatr* 2002;161(4):196–201.
353. Ozkaya O, Soylemezoglu O, Gonen S, et al. Renin-angiotensin system gene polymorphisms: association with susceptibility to

- Henoch-Schönlein purpura and renal involvement. *Clin Rheumatol* 2006;25(6):861-5.
354. Dudley J, Afifi E, Gardner A, et al. Polymorphism of the ACE gene in Henoch-Schönlein purpura nephritis. *Pediatr Nephrol* 2000;14(3):218-20.
 355. Ozcakar ZB, Yalcinkaya F, Cakar N, et al. MEFV mutations modify the clinical presentation of Henoch-Schönlein purpura. *J Rheumatol* 2008;35(12):2427-9.
 356. Huber AM, King J, McLaine P, et al. A randomized, placebo-controlled trial of prednisone in early Henoch Schönlein Purpura [ISRCTN85109383]. *BMC Med* 2004;2:7.
 357. Chartapisak W, Opastirakul S, Hodson EM, et al. Interventions for preventing and treating kidney disease in Henoch-Schönlein Purpura (HSP). *Cochrane Database Syst Rev* 2009;(3):CD005128.
 358. Narchi H. Risk of long term renal impairment and duration of follow up recommended for Henoch-Schönlein purpura with normal or minimal urinary findings: a systematic review. *Arch Dis Child* 2005;90(9):916-20.
 359. Chantorn R, Lim HW, Shwayder TA. Photosensitivity disorders in children: part II. *J Am Acad Dermatol* 2012;67(6):1113 e1-15; quiz 28, 27.
 360. Chantorn R, Lim HW, Shwayder TA. Photosensitivity disorders in children: part I. *J Am Acad Dermatol* 2012;67(6):1093 e1-18; quiz 111-2.
 361. Yesudian PD, Sharpe GR. Hydroa vacciniforme with oral mucosal involvement. *Pediatr Dermatol* 2004;21(5):555-7.
 362. Lysell J, Wiegleb Edstrom D, et al. Antiviral therapy in children with hydroa vacciniforme. *Acta Derm Venereol* 2009;89(4):393-7.
 363. Iwatsuki K, Xu Z, Takata M, et al. The association of latent Epstein-Barr virus infection with hydroa vacciniforme. *Br J Dermatol* 1999;140(4):715-21.
 364. Sunohara A, Mizuno N, Sakai M, et al. Action spectrum for UV erythema and reproduction of the skin lesions in hydroa vacciniforme. *Photodermatology* 1988;5(3):139-45.
 365. Sonnex TS, Hawk JL. Hydroa vacciniforme: a review of ten cases. *Br J Dermatol* 1988;118(1):101-8.
 366. Xu Z, Lian S. Epstein-Barr virus-associated hydroa vacciniforme-like cutaneous lymphoma in seven Chinese children. *Pediatr Dermatol* 2010;27(5):463-9.
 367. Iwatsuki K, Satoh M, Yamamoto T, et al. Pathogenic link between hydroa vacciniforme and Epstein-Barr virus-associated hematologic disorders. *Arch Dermatol* 2006;142(5):587-95.
 368. Menage HD, Vaughan RW, Baker CS, et al. HLA-DR4 may determine expression of actinic prurigo in British patients. *J Invest Dermatol* 1996;106(2):362-7.
 369. Sheridan DP, Lane PR, Irvine J, et al. HLA typing in actinic prurigo. *J Am Acad Dermatol* 1990;22(6 Pt 1):1019-23.
 370. Magana M, Mendez Y, Rodriguez A, et al. The conjunctivitis of solar (actinic) prurigo. *Pediatr Dermatol* 2000;17(6):432-5.
 371. Herrera-Geopfert R, Magana M. Follicular cheilitis. A distinctive histopathologic finding in actinic prurigo. *Am J Dermatopathol* 1995;17(4):357-61.
 372. Crouch R, Foley P, Baker C. Actinic prurigo: a retrospective analysis of 21 cases referred to an Australian photobiology clinic. *Australas J Dermatol* 2002;43(2):128-32.
 373. Farr PM, Diffey BL. Treatment of actinic prurigo with PUVA: mechanism of action. *Br J Dermatol* 1989;120(3):411-18.
 374. Lane PR, Moreland AA, Hogan DJ. Treatment of actinic prurigo with intermittent short-course topical 0.05% clobetasol 17-propionate. A preliminary report. *Arch Dermatol* 1990;126(9):1211-13.
 375. Kerr A, Ferguson J. Photoallergic contact dermatitis. *Photodermatol Photoimmunol Photomed* 2010;26(2):56-65.
 376. Foley P, Zuo Y, Plunkett A, et al. The frequency of common skin conditions in preschool-aged children in Australia: seborrheic dermatitis and pityriasis capitis (cradle cap). *Arch Dermatol* 2003;139(3):318-22.
 377. Avenel-Audran M, Dutartre H, Goossens A, et al. Octocrylene, an emerging photoallergen. *Arch Dermatol* 2010;146(7):753-7.
 378. Wang L, Sterling B, Don P. Berloque dermatitis induced by 'Florida water'. *Cutis* 2002;70(1):29-30.
 379. Gould JW, Mercurio MG, Elmets CA. Cutaneous photosensitivity diseases induced by exogenous agents. *J Am Acad Dermatol* 1995;33(4):551-73; quiz 74-6.
 380. Gruson LM, Chang MW. Berloque dermatitis mimicking child abuse. *Arch Pediatr Adolesc Med* 2002;156(11):1091-3.
 381. Goskovic MO, Friedlander SF, Eichenfield LF. Endemic 'lime' disease: phytophotodermatitis in San Diego County. *Pediatrics* 1994;93(5):828-30.
 382. Carlsen K, Weismann K. Phytophotodermatitis in 19 children admitted to hospital and their differential diagnoses: Child abuse and herpes simplex virus infection. *J Am Acad Dermatol* 2007;57(5 Suppl):S88-91.
 383. Frick MA, Soler-Palacin P, Martin Nalda A, et al. Photosensitivity in immunocompromised patients receiving long-term therapy with oral voriconazole. *Pediatr Infect Dis J* 2010;29(5):480-1.
 384. Kearns GL, Williams BJ, Timmons OD. Fluorescein phototoxicity in a premature infant. *J Pediatr* 1985;107(5):796-8.
 385. Porat R, Gilbert S, Magilner D. Methylene blue-induced phototoxicity: an unrecognized complication. *Pediatrics* 1996;97(5):717-21.
 386. Ahmed I. Childhood porphyrias. *Mayo Clin Proc* 2002;77:825-36.
 387. Gross U, Hoffmann GF, Doss MO. Erythropoietic and hepatic porphyrias. *J Inher Metab Dis* 2000;23:641-61.
 388. Kauppinen R. Porphyrias. *Lancet* 2005;365:241-52.
 389. Mascaro JM. Porphyrias in children. *Pediatr Dermatol* 1992;9:371-2.
 390. Lim HW. Porphyria update. *Pediatr Dermatol* 2000;17:75-83.
 391. Lim HW, Cohen JL. The cutaneous porphyrias. *Semin Cutan Med Surg* 1999;18:285-92.
 392. Jensen JD, Resnick SD. Porphyria in childhood. *Semin Dermatol* 1995;14:33-9.
 393. Murphy GM. The cutaneous porphyrias: a review. *British Photodermatology Group. Br J Dermatol* 1999;140:573-81.
 394. Elder GH. Update on enzyme and molecular defects in porphyria. *Photodermatol Photoimmunol Photomed* 1998;14:66-9.
 395. Lim HW. Pathogenesis of photosensitivity in the cutaneous porphyrias. *J Invest Dermatol* 2005;124:xvi-xvii.
 396. Poh-Fitzpatrick MB. Molecular and cellular mechanisms of porphyrin photosensitization. *Photodermatol* 1986;3:148-57.
 397. Poh-Fitzpatrick MB. Clinical features of the porphyrias. *Clin Dermatol* 1998;16:251-64.
 398. Lim HW, Murphy GM. The porphyrias. *Clin Dermatol* 1996;14:375-87.
 399. Fritsch C, Bolsen K, Ruzicka T, et al. Congenital erythropoietic porphyria. *J Am Acad Dermatol* 1997;36:594-610.
 400. Huang JL, Zaider E, Roth P, et al. Congenital erythropoietic porphyria: clinical, biochemical, and enzymatic profile of a severely affected infant. *J Am Acad Dermatol* 1996;34:924-7.
 401. Hogeling M, Nakano T, Dvorak CC, et al. Severe neonatal congenital erythropoietic porphyria. *Pediatr Dermatol* 2011;28:416-20.
 402. Berry AA, Desnick RJ, Astrin KH, et al. Two brothers with mild congenital erythropoietic porphyria due to a novel genotype. *Arch Dermatol* 2005;141:1575-9.
 403. Venkatesh P, Garg SP, Kumaran E, et al. Congenital porphyria with necrotizing scleritis in a 9-year-old child. *Clin Exp Ophthalmol* 2000;28:314-18.
 404. Fontanellas A, Bensidhoum M, Enriquez de SR, et al. A systematic analysis of the mutations of the uroporphyrinogen III synthase gene in congenital erythropoietic porphyria. *Eur J Hum Genet* 1996;4:274-82.
 405. Desnick RJ, Astrin KH. Congenital erythropoietic porphyria: advances in pathogenesis and treatment. *Br J Haematol* 2002;117:779-95.
 406. Xu W, Astrin KH, Desnick RJ. Molecular basis of congenital erythropoietic porphyria: mutations in the human uroporphyrinogen III synthase gene. *Hum Mutat* 1996;7:187-92.
 407. Kaiser IH. Brown amniotic fluid in congenital erythropoietic porphyria. *Obstet Gynecol* 1980;56:383-4.
 408. Lazebnik N, Lazebnik RS. The prenatal presentation of congenital erythropoietic porphyria: report of two siblings with elevated maternal serum alpha-fetoprotein. *Prenat Diagn* 2004;24:282-6.
 409. Ikha-Dahmane F, Dommergues M, Narcy F, et al. Congenital erythropoietic porphyria: prenatal diagnosis and autopsy findings in two sibling fetuses. *Pediatr Dev Pathol* 2001;4:180-4.
 410. Ged C, Moreau-Gaudry F, Taine L, et al. Prenatal diagnosis in congenital erythropoietic porphyria by metabolic measurement and DNA mutation analysis. *Prenat Diagn* 1996;16:83-6.
 411. Dawe SA, Peters TJ, Du VA, et al. Congenital erythropoietic porphyria: dilemmas in present day management. *Clin Exp Dermatol* 2002;27:680-3.
 412. Guarini L, Piomelli S, Poh-Fitzpatrick MB. Hydroxyurea in congenital erythropoietic porphyria. *N Engl J Med* 1994;330:1091-2.
 413. Piomelli S, Poh-Fitzpatrick MB, Seaman C, et al. Complete suppression of the symptoms of congenital erythropoietic porphyria by long-term treatment with high-level transfusions. *N Engl J Med* 1986;314:1029-31.
 414. Gorchein A, Guo R, Lim CK, et al. Porphyrins in urine, plasma, erythrocytes, bile and faeces in a case of congenital erythropoietic porphyria (Gunther's disease) treated with blood transfusion and iron chelation: lack of benefit from oral charcoal. *Biomed Chromatogr* 1998;12:350-6.
 415. Minder EI, Schneider-Yin X, Moll F. Lack of effect of oral charcoal in congenital erythropoietic porphyria. *N Engl J Med* 1994;330:1092-4.

416. Hift RJ, Meissner PN, Kirsch RE. The effect of oral activated charcoal on the course of congenital erythropoietic porphyria. *Br J Dermatol* 1993;129:14–17.
417. Pimstone NR, Gandhi SN, Mukerji SK. Therapeutic efficacy of oral charcoal in congenital erythropoietic porphyria. *N Engl J Med* 1987;316:390–3.
418. Maleville J, Babin JP, Mollard S, et al. Porphyrie erythropoietique congenitale de Gunther et carotenoides. Essai thérapeutique de 4 ans. *Ann Dermatol Venerol* 1982;109:883–7.
419. Seip M, Thune PO, Eriksen L. Treatment of photosensitivity in congenital erythropoietic porphyria (CEP) with beta-carotene. *Acta Derm Venerol* 1974;54:239–40.
420. Tezcan I, Xu W, Gurgey A, et al. Congenital erythropoietic porphyria successfully treated by allogeneic bone marrow transplantation. *Blood* 1998;92:4053–8.
421. Thomas C, Ged C, Nordmann Y, et al. Correction of congenital erythropoietic porphyria by bone marrow transplantation. *J Pediatr* 1996;129:453–6.
422. Shaw PH, Mancini AJ, McConnell JB, et al. Treatment of congenital erythropoietic porphyria in children by allogeneic stem cell transplantation: a case report and review of the literature. *Bone Marrow Transplant* 2001;27:101–5.
423. Harada FA, Shwayder TA, Desnick RJ, et al. Treatment of severe congenital erythropoietic porphyria by bone marrow transplantation. *J Am Acad Dermatol* 2001;45:279–82.
424. Dupuis-Girod S, Akkari V, Ged C, et al. Successful match-unrelated donor bone marrow transplantation for congenital erythropoietic porphyria (Gunther disease). *Eur J Pediatr* 2005;164:104–7.
425. DeLeo VA, Poh-Fitzpatrick M, Mathews-Roth M, et al. Erythropoietic protoporphyria. 10 years' experience. *Am J Med* 1976;60:8–22.
426. Whatley SD, Mason NG, Khan M, et al. Autosomal recessive erythropoietic protoporphyria in the United Kingdom: prevalence and relationship to liver disease. *J Med Genet* 2004;41:e105.
427. Goerz G, Bunselmeyer S, Bolsen K, et al. Ferrochelatase activities in patients with erythropoietic protoporphyria and their families. *Br J Dermatol* 1996;134:880–5.
428. Norris PG, Nunn AV, Hawk JL, et al. Genetic heterogeneity in erythropoietic protoporphyria: a study of the enzymatic defect in nine affected families. *J Invest Dermatol* 1990;95:260–3.
429. Sarkany RP, Alexander GJ, Cox TM. Recessive inheritance of erythropoietic protoporphyria with liver failure. *Lancet* 1994;344:958–9.
430. Frank J, Nelson J, Wang X, et al. Erythropoietic protoporphyria: identification of novel mutations in the ferrochelatase gene and comparison of biochemical markers versus molecular analysis as diagnostic strategies. *J Invest Med* 1999;47:278–84.
431. Mathews-Roth MM. The treatment of erythropoietic protoporphyria. *Semin Liver Dis* 1998;18:425–6.
432. Todd DJ. Therapeutic options for erythropoietic protoporphyria. *Br J Dermatol* 2000;142:826–7.
433. Murphy GM. Diagnosis and management of the erythropoietic porphyrias. *Dermatol Ther* 2003;16:57–64.
434. Miao LL, Mathews-Roth MM, Poh-Fitzpatrick MB. Beta carotene treatment and erythrocytic protoporphyrin levels. *Arch Dermatol* 1979;115:818.
435. Mathews-Roth MM. Erythropoietic protoporphyria: treatment with antioxidants and potential cure with gene therapy. *Methods Enzymol* 2000;319:479–84.
436. Warren LJ, George S. Erythropoietic protoporphyria treated with narrow-band (TL-01) UVB phototherapy. *Australas J Dermatol* 1998;39:179–82.
437. Gorchein A, Foster GR. Liver failure in protoporphyria: long-term treatment with oral charcoal. *Hepatology* 1999;29:995–6.
438. Elder GH, Smith SG, Herrero C, et al. Hepatoerythropoietic porphyria: a new uroporphyrinogen decarboxylase defect or homozygous porphyria cutanea tarda? *Lancet* 1981;1:916–19.
439. Lim HW, Poh-Fitzpatrick MB. Hepatoerythropoietic porphyria: a variant of childhood-onset porphyria cutanea tarda. Porphyrin profiles and enzymatic studies of two cases in a family. *J Am Acad Dermatol* 1984;11:1103–11.
440. Piñol-Aguade J, Herrero C, Almeida J, et al. Porphyrie hepato-erythroaire, une nouvelle forme de porphyrie. *Ann Dermatol Syphiligr* 1975;102:129–36.
441. Toback AC, Sassa S, Poh-Fitzpatrick MB, et al. Hepatoerythropoietic porphyria: clinical, biochemical, and enzymatic studies in a three-generation family lineage. *N Engl J Med* 1987;316:645–50.
442. Elder GH. Hepatic porphyrias in children. *J Inher Metab Dis* 1997;20:237–46.
443. Thunell S, Holmberg L, Lundgren J. Aminolaevulinate dehydratase porphyria in infancy. A clinical and biochemical study. *J Clin Chem Clin Biochem* 1987;25:5–14.
444. Thunell S, Henrichson A, Floderus Y, et al. Liver transplantation in a boy with acute porphyria due to aminolaevulinate dehydratase deficiency. *Eur J Clin Chem Clin Biochem* 1992;30:599–606.
445. Lee DS, Flachsova E, Bodnarova M, et al. Structural basis of hereditary coproporphyria. *Proc Natl Acad Sci USA* 2005;102:14232–7.
446. Lamoril J, Puy H, Whatley SD, et al. Characterization of mutations in the CPO gene in British patients demonstrates absence of genotype-phenotype correlation and identifies relationship between hereditary coproporphyria and harderoporphyria. *Am J Hum Genet* 2001;68:1130–8.
447. Lamoril J, Martasek P, Deybach JC, et al. A molecular defect in coproporphyrinogen oxidase gene causing harderoporphyria, a variant form of hereditary coproporphyria. *Hum Mol Genet* 1995;4:275–8.
448. Nordmann Y, Grandchamp B, de VH, et al. Harderoporphyria: a variant hereditary coproporphyria. *J Clin Invest* 1983;72:1139–49.
449. Palmer RA, Elder GH, Barrett D, et al. Homozygous variegate porphyria: a compound heterozygote with novel mutations in the protoporphyrinogen oxidase gene. *Br J Dermatol* 2001;144:866–9.
450. Kauppinen R, Timonen K, von M, et al. Homozygous variegate porphyria: 20 year follow-up and characterization of molecular defect. *J Invest Dermatol* 2001;116:610–13.
451. Roberts AG, Puy H, Dailey TA, et al. Molecular characterization of homozygous variegate porphyria. *Hum Mol Genet* 1998;7:1921–5.
452. Crawford GH, Kim S, James WD. Skin signs of systemic disease: an update. *Adv Dermatol* 2002;18:1–27.
453. Mallon E, Wojnarowska F, Hope P, et al. Neonatal bullous eruption as a result of transient porphyria in a premature infant with hemolytic disease of the newborn. *J Am Acad Dermatol* 1995;33:333–6.
454. Paller AS, Eramo LR, Farrell EE, et al. Purpuric phototherapy-induced eruption in transfused neonates: relation to transient porphyria. *Pediatrics* 1997;100:360–4.
455. Vanden Eijnden S, Blum D, Clercx A, et al. Cutaneous porphyria in a neonate with tyrosinaemia type I. *Eur J Pediatr* 2000;159:503–6.
456. Lowry RB. Early onset of Cockayne syndrome. *Am J Med Genet* 1982;13(2):209–10.
457. Rapin I, Lindenbaum Y, Dickson DW, et al. Cockayne syndrome and xeroderma pigmentosum. *Neurology* 2000;55(10):1442–9.
458. Nance MA, Berry SA. Cockayne syndrome: review of 140 cases. *Am J Med Genet* 1992;42(1):68–84.
459. Stefanini M, Fawcett H, Botta E, et al. Genetic analysis of twenty-two patients with Cockayne syndrome. *Hum Genet* 1996;97(4):418–23.
460. Crovato F, Borroni C, Rebori A. Trichothiodystrophy – BIDS, IBIDS and PIBIDS? *Br J Dermatol* 1983;108(2):247.
461. Faghri S, Tamura D, Kraemer KH, et al. Trichothiodystrophy: a systematic review of 112 published cases characterises a wide spectrum of clinical manifestations. *J Med Genet* 2008;45(10):609–21.
462. Liang C, Kraemer KH, Morris A, et al. Characterization of tiger-tail banding and hair shaft abnormalities in trichothiodystrophy. *J Am Acad Dermatol* 2005;52(2):224–32.
463. Nakazawa Y, Sasaki K, Mitsutake N, et al. Mutations in UVSSA cause UV-sensitive syndrome and impair RNA polymerase II processing in transcription-coupled nucleotide-excision repair. *Nat Genet* 2012;44(5):586–92.
464. Nardo T, Oneda R, Spivak G, et al. A UV-sensitive syndrome patient with a specific CSA mutation reveals separable roles for CSA in response to UV and oxidative DNA damage. *Proc Natl Acad Sci U S A* 2009;106(15):6209–14.
465. Vennos EM, Collins M, James WD. Rothmund-Thomson syndrome: review of the world literature. *J Am Acad Dermatol* 1992;27(5 Pt 1):750–62.
466. Larizza L, Roversi G, Volpi L. Rothmund-Thomson syndrome. *Orphanet J Rare Dis* 2010;5:2.
467. Wang LL, Levy ML, Lewis RA, et al. Clinical manifestations in a cohort of 41 Rothmund-Thomson syndrome patients. *Am J Med Genet* 2001;102(1):11–17.
468. Stinco G, Governatori G, Mattighello P, et al. Multiple cutaneous neoplasms in a patient with Rothmund-Thomson syndrome: case report and published work review. *J Dermatol* 2008;35(3):154–61.
469. Howell SM, Bray DW. Amelanotic melanoma in a patient with Rothmund-Thomson syndrome. *Arch Dermatol* 2008;144(3):416–17.
470. Kitao S, Shimamoto A, Goto M, et al. Mutations in RECQL4 cause a subset of cases of Rothmund-Thomson syndrome. *Nat Genet* 1999;22(1):82–4.
471. German J. Bloom's syndrome. *Dermatol Clin* 1995;13(1):7–18.
472. German J. Bloom's syndrome. XX. The first 100 cancers. *Cancer Genet Cytogenet* 1997;93(1):100–6.
473. Lai-Cheong JE, McGrath JA. Kindler syndrome. *Dermatol Clin* 2010;28(1):119–24.

474. Has C, Castiglia D, del Rio M, et al. Kindler syndrome: extension of FERMT1 mutational spectrum and natural history. *Hum Mutat* 2011;32(11):1204–12.
475. Jobard F, Bouadjar B, Caux F, et al. Identification of mutations in a new gene encoding a FERM family protein with a pleckstrin homology domain in Kindler syndrome. *Hum Mol Genet* 2003;12(8):925–35.
476. Nowaczyk MJ, Irons MB. Smith-Lemli-Opitz syndrome: phenotype, natural history, and epidemiology. *Am J Med Genetics C, Semin Med Genet* 2012;160C(4):250–62.
477. Anstey AV, Ryan A, Rhodes LE, et al. Characterization of photosensitivity in the Smith-Lemli-Opitz syndrome: a new congenital photosensitivity syndrome. *Br J Dermatol* 1999;141(3):406–14.
478. Wassif CA, Maslen C, Kachilele-Linjewile S, et al. Mutations in the human sterol delta7-reductase gene at 11q12–11q13 cause Smith-Lemli-Opitz syndrome. *Am J Hum Genet* 1998;63(1):55–62.
479. Waterham HR, Wijburg FA, Hennekam RC, et al. Smith-Lemli-Opitz syndrome is caused by mutations in the 7-dehydrocholesterol reductase gene. *Am J Hum Genet* 1998;63(2):329–38.
480. Nozaki J, Dakeishi M, Ohura T, et al. Homozygosity mapping to chromosome 5p15 of a gene responsible for Hartnup disorder. *Biochem Biophys Res Commun* 2001;284(2):255–60.
481. Seow HF, Broer S, Broer A, et al. Hartnup disorder is caused by mutations in the gene encoding the neutral amino acid transporter SLC6A19. *Nat Genet* 2004;36(9):1003–7.
482. Baron DN, Dent CE, Harris H, et al. Hereditary pellagra-like skin rash with temporary cerebellar ataxia, constant renal amino-aciduria, and other bizarre biochemical features. *Lancet* 1956;271(6940):421–8.
483. Symula DJ, Shedlovsky A, Guillery EN, et al. A candidate mouse model for Hartnup disorder deficient in neutral amino acid transport. *Mamm Genome* 1997;8(2):102–7.
484. Lee MH, Barnett PL. Petechiae/purpura in well-appearing infants. *Pediatr Emerg Care* 2012;28:503–5.
485. Bowden JB, Hebert AA, Rapini RP. Dermal hematopoiesis in neonates: report of five cases. *J Am Acad Dermatol* 1989;20:1104–10.
486. Brough AJ, Jones D, Page RH, et al. Dermal erythropoiesis in neonatal infants: a manifestation of intrauterine viral disease. *Pediatrics* 1967;40:627–35.
487. Klein HZ, Markarian M. Dermal erythropoiesis in congenital rubella. Description of an infected newborn who had purpura associated with marked extramedullary erythropoiesis in the skin and elsewhere. *Clin Pediatr (Phila)* 1969;8:604–7.
488. Evole-Buselli M, Hernandez-Marti MJ, Gascó-Lacalle B, et al. Neonatal dermal hematopoiesis associated with diffuse neonatal hemangiomatosis. *Pediatr Dermatol* 1997;14:383–6.
489. Shih YL, Kuo TT, Weng YH, et al. Coexisting metastatic neuroblastoma and dermal erythropoiesis in a blueberry muffin baby. *J Am Acad Dermatol* 2011;64:1197–8.
490. Holland KE, Galbraith SS, Drolet BA. Neonatal violaceous skin lesions: expanding the differential of the 'blueberry muffin baby'. *Adv Dermatol* 2005;21:153–92.
491. Silver MM, Hellmann J, Zielenska M, et al. Anemia, blueberry-muffin rash, and hepatomegaly in a newborn infant. *J Pediatr* 1996;128:579–86.
492. Hebert AA, Esterly NB, Gardner TH. Dermal erythropoiesis in Rh hemolytic disease of the newborn. *J Pediatr* 1985;107:799–801.
493. Argyle JC, Zone JJ. Dermal erythropoiesis in a neonate. *Arch Dermatol* 1981;117:492–4.
494. Pandey V, Dummula K, Fraga G, et al. Late-onset blueberry muffin lesions following recombinant erythropoietin administration in a premature infant. *J Pediatr Hematol Oncol* 2012;34(7):534–5.
495. Hawthorne HC Jr, Nelson JS, Witzleben CL, et al. Blanching subcutaneous nodules in neonatal neuroblastoma. *J Pediatr* 1970;77:297–300.
496. Shown TE, Durfee MF. Blueberry muffin baby: neonatal neuroblastoma with subcutaneous metastases. *J Urol* 1970;104:193–5.
497. van Erp IE. Cutaneous metastases in neuroblastoma. *Dermatologica* 1968;136:265–9.
498. Kitagawa N, Arata J, Ohtsuki Y, et al. Congenital alveolar rhabdomyosarcoma presenting as a blueberry muffin baby. *J Dermatol* 1989;16:409–11.
499. Resnik KS, Brod BB. Leukemia cutis in congenital leukemia. Analysis and review of the world literature with report of an additional case. *Arch Dermatol* 1993;129:1301–6.
500. Enjolras O, Leibowitch M, Bonacini F, et al. Histiocytoses langerhansiennes congenitales cutanees. A propos de 7 cas. *Ann Dermatol Venerol* 1992;119:111–17.
501. Price VE, Ledingham DL, Krümpel A, et al. Diagnosis and management of neonatal purpura fulminans. *Semin Fetal Neonatal Med* 2011;16:318–22.
502. Chalmers E, Cooper P, Forman K, et al. Purpura fulminans: recognition, diagnosis and management. *Arch Dis Child* 2011;96:1066–71.
503. Tuddenham EG, Takase T, Thomas AE, et al. Homozygous protein C deficiency with delayed onset of symptoms at 7 to 10 months. *Thromb Res* 1989;53:475–84.
504. Pipe SW, Schmaier AH, Nichols WC, et al. Neonatal purpura fulminans in association with factor V R506Q mutation. *J Pediatr* 1996;128:706–9.
505. Marlar RA, Neumann A. Neonatal purpura fulminans due to homozygous protein C or protein S deficiencies. *Semin Thromb Hemost* 1990;16:299–309.
506. Marciniak E, Wilson HD, Marlar RA. Neonatal purpura fulminans: a genetic disorder related to the absence of protein C in blood. *Blood* 1985;65:15–20.
507. Seligsohn U, Berger A, Abend M, et al. Homozygous protein C deficiency manifested by massive venous thrombosis in the newborn. *N Engl J Med* 1984;310:559–62.
508. Sills RH, Marlar RA, Montgomery RR, et al. Severe homozygous protein C deficiency. *J Pediatr* 1984;105:409–13.
509. Marlar RA, Montgomery RR, Broekmans AW. Diagnosis and treatment of homozygous protein C deficiency. Report of the Working Party on Homozygous Protein C Deficiency of the Subcommittee on Protein C and Protein S, International Committee on Thrombosis and Haemostasis. *J Pediatr* 1989;114:528–34.
510. Chuansumrit A, Hotrakitya S, Kruavit A. Severe acquired neonatal purpura fulminans. *Clin Pediatr (Phila)* 1996;35:373–6.
511. Gurses N, Islek I. Causes of purpura fulminans. *Pediatr Infect Dis J* 1995;14:552–3.
512. Petaja J, Manco-Johnson MJ. Protein C pathway in infants and children. *Semin Thromb Hemost* 2003;29:349–62.
513. Aiach M, Borgel D, Gaussem P, et al. Protein C and protein S deficiencies. *Semin Hematol* 1997;34:205–16.
514. Grundy CB, Melissari E, Lindo V, et al. Late-onset homozygous protein C deficiency. *Lancet* 1991;338:575–6.
515. Tripodi A, Franchi F, Krachmalnicoff A, et al. Asymptomatic homozygous protein C deficiency. *Acta Haematol* 1990;83:152–5.
516. Mahasandana C, Suvatte V, Chuansumrit A, et al. Homozygous protein S deficiency in an infant with purpura fulminans. *J Pediatr* 1990;117:750–3.
517. Gomez E, Ledford MR, Pegelow CH, et al. Homozygous protein S deficiency due to a one base pair deletion that leads to a stop codon in exon III of the protein S gene. *Thromb Haemost* 1994;71:723–6.
518. Dahlback B. The discovery of activated protein C resistance. *J Thromb Haemost* 2003;1:3–9.
519. Dahlback B. Blood coagulation and its regulation by anticoagulant pathways: genetic pathogenesis of bleeding and thrombotic diseases. *J Intern Med* 2005;257:209–23.
520. Adcock DM, Hicks MJ. Dermatopathology of skin necrosis associated with purpura fulminans. *Semin Thromb Hemost* 1990;16:283–92.
521. Minutillo C, Pemberton PJ, Willoughby ML, et al. Neonatal purpura fulminans and transient protein C deficiency. *Arch Dis Child* 1990;65:561–2.
522. Baliga V, Thwaites R, Tillyer ML, et al. Homozygous protein C deficiency – management with protein C concentrate. *Eur J Pediatr* 1995;154:534–8.
523. Dreyfus M, Masterson M, David M, et al. Replacement therapy with a monoclonal antibody purified protein C concentrate in newborns with severe congenital protein C deficiency. *Semin Thromb Hemost* 1995;21:371–81.
524. Angelis M, Pegelow CH, Khan FA, et al. En bloc heterotopic auxiliary liver and bilateral renal transplant in a patient with homozygous protein C deficiency. *J Pediatr* 2001;138:120–2.
525. Casella JE, Lewis JH, Bontempo FA, et al. Successful treatment of homozygous protein C deficiency by hepatic transplantation. *Lancet* 1988;1:435–8.
526. Crawford RI, Lawlor ER, Wadsworth LD, et al. Transient erythroporphyria of infancy. *J Am Acad Dermatol* 1996;35:833–4.
527. Siegfried EC, Stone MS, Madison KC. Ultraviolet light burn: a cutaneous complication of visible light phototherapy of neonatal jaundice. *Pediatr Dermatol* 1992;9:278–82.
528. George M. Methylene-blue-induced hyperbilirubinemia and phototoxicity in a neonate. *Clin Pediatr (Phila)* 2000;39:659–61.
529. Burry JN, Lawrence JR. Phototoxic blisters from high frusemide dosage. *Br J Dermatol* 1976;94:495–9.
530. Torrelo A, Requena C, Mediero IG, et al. Schamberg's purpura in children: A review of 13 cases. *J Am Acad Dermatol* 2003;48:31–3.
531. Zvulunov A, Avinoach I, Hatskelzon L, et al. Pigmented purpuric dermatosis (Schamberg's

- purpura) in an infant. *Dermatol Online J* 1999;5:2.
532. Sethuraman G, Sugandhan S, Bansal A, et al. Familial pigmented purpuric dermatoses. *J Dermatol* 2006;33:639–41.
533. Nagata K, Danno K, Tanaka S. Unilateral Schamberg disease in a 14-year-old Japanese boy. *J Dermatol* 1999;26:348–51.
534. Bell HK, Dobson CM, Jackson SP, et al. Localized morphoea preceded by a pigmented purpuric dermatosis. *Clin Exp Dermatol* 2003;28:369–71.
535. Ugajin T, Satoh T, Yokozeki H, et al. Mycosis fungoides presenting as pigmented purpuric eruption. *Eur J Dermatol* 2005;15:489–91.
536. Milea M, Dimov HA, Cribier B. Generalized Schamberg's disease treated with PUVA in a child. *Ann Dermatol Venereol* 2007;134:378–80.

Infantile Hemangiomas and Other Vascular Tumors

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Infantile hemangioma

Infantile hemangioma (IH) is the most common vascular tumor encountered during early infancy. It is a benign proliferation of endothelial cells that characteristically undergoes a phase of rapid growth followed by slow spontaneous involution. Although large population-based studies are lacking, infantile hemangiomas are estimated to occur in 2.6–5% of infants.^{1,2} The incidence is highest among Caucasian infants with lower rates in African-American, Hispanic, and Asian infants.³ Females are more commonly affected than males at ratios of 2–3:1, with the female-to-male ratio approximately 9:1 in patients with segmental hemangiomas associated with PHACE syndrome.^{4,5}

Caucasian race, prematurity and low birthweight are well-established risk factors for the development of IH.^{3,6} The risk of IH increases by 40% for every 500 g decrease in birthweight.⁷ A prospective study of over 1000 children with infantile hemangiomas identified additional risk factors, including multiple gestation pregnancies, advanced maternal age, and pregnancies complicated with pre-eclampsia or placenta previa.^{5,8} Placental abnormalities that impair utero-placental circulation, including retroplacental hematoma, ischemic infarction, dilated vascular communications, vasculitis and chorioamnionitis have been observed to be more common in infants with IH.⁹ An earlier study reported a threefold increased incidence of hemangiomas in infants born to mothers who undergo chorionic villus sampling, compared with those whose mothers undergo amniocentesis, but subsequent studies have not been conclusive.¹⁰ In-vitro fertilization has been suggested as a possible risk factor in one study.² The majority of hemangiomas arise sporadically; however, a family history can be elicited in some patients, and autosomal dominant transmission has been reported.¹¹

CLINICAL SUBTYPES

Infantile hemangiomas can be classified based on their location within the skin: superficial, deep, and mixed (superficial and deep). Superficial hemangiomas are the most common type, occurring in approximately 50–60% of cases. Mixed-type IH are estimated to occur in 25–35% of cases, and deep hemangiomas in 15%.¹² Superficial hemangiomas are typically bright red with a lobulated surface. These characteristics have led to the use of the term ‘strawberry’ hemangioma. Deep hemangiomas are not commonly noted in the neonatal period, often appearing at 1–3 months of life, or later, as a warm, subcutaneous mass caused by proliferation of the tumor in the deeper portion of the dermis or subcutis. The overlying skin may appear normal or have relatively inconspicuous superficial changes, such as faint

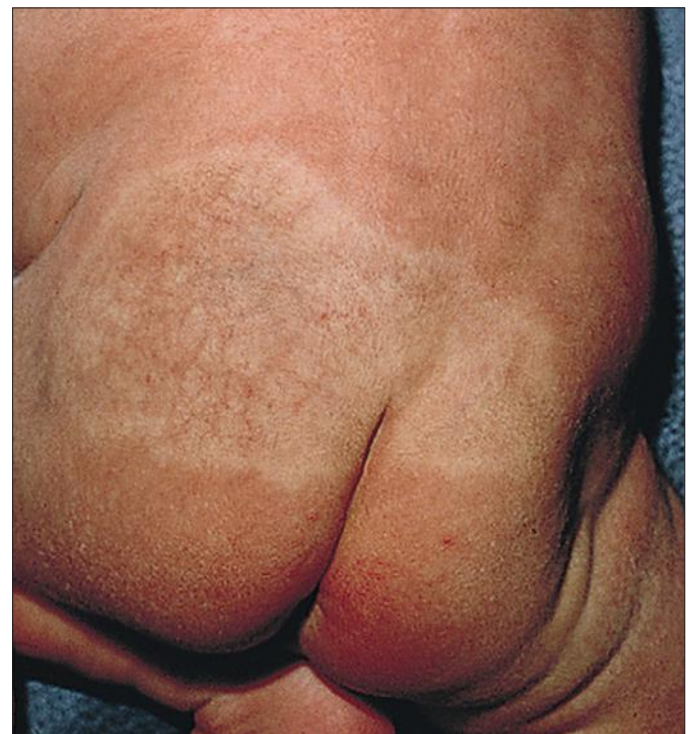
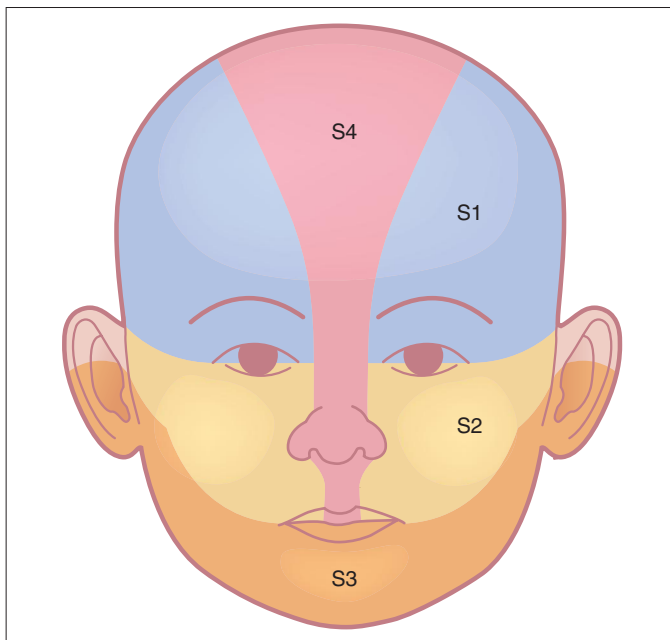
blue color, telangiectasias or dilated veins. Mixed-type hemangiomas frequently exhibit a configuration resembling a poached egg, with a well-circumscribed red superficial portion overlying a less well-defined bluish to violaceous deeper component.

In addition to characterizing hemangiomas according to their *depth* and *location* within the skin, the *pattern of involvement* is a predictor of prognosis and risk for associated complications.⁵ Described patterns include ‘focal’, or localized, lesions that appear to arise from a central point, and ‘segmental’ lesions, which typically encompass a larger territory of skin, which in some anatomic sites clearly corresponds to a developmental subunit (Fig. 21.1).^{13,14} Some lesions are difficult to classify as either focal or segmental and are thus designated ‘indeterminate’. Segmental lesions more often require treatment and are more likely to be associated with complications, including underlying extracutaneous anomalies, including spinal dysraphism, genitourinary anomalies, and PHACE syndrome.¹⁴ The patterns of segmental hemangiomas correspond to known embryologic prominences, suggesting a neuroectodermal derivation for their distribution.¹⁵ The frontotemporal (S1), maxillary (S2), mandibular (S3), and frontonasal (S4) segments designate commonly observed patterns of facial hemangiomas (Fig. 21.2).¹⁵

NATURAL HISTORY

Infantile hemangiomas have a characteristic clinical course marked by rapid early proliferation, slower late proliferation, a plateau phase, and finally gradual involution. They are either present at birth or appear in the first few weeks of life. Precursor lesions (or so-called ‘premonitory marks’) are seen in as many as 65% of patients and may appear as discrete fine telangiectasias superimposed on a background of pallor, a faint erythematous patch, or a bruise-like area (Fig. 21.3).¹⁶ It may be difficult initially to differentiate an erythematous hemangioma precursor from a capillary malformation, but clues include a more ill-defined border, fine telangiectasias, and, if present, skin ulceration. Serial examinations may be necessary to establish the correct diagnosis. Rarely, a hemangioma on the perineum or lip may present in the neonate with ulceration, without an obvious hemangioma, mimicking bacterial or herpetic infection. In these cases, the hemangioma becomes evident over the subsequent days to weeks (see Chapters 10 and 17).

In the first few weeks of life, most infantile hemangiomas proliferate rapidly; 80% of superficial hemangioma growth occurs before 3 months of age, with a period of accelerated growth between 5 and 7 weeks of age.^{16,17} The late proliferative stage is marked by slower growth, but is more variable in its duration, with certain subsets of hemangiomas, including those



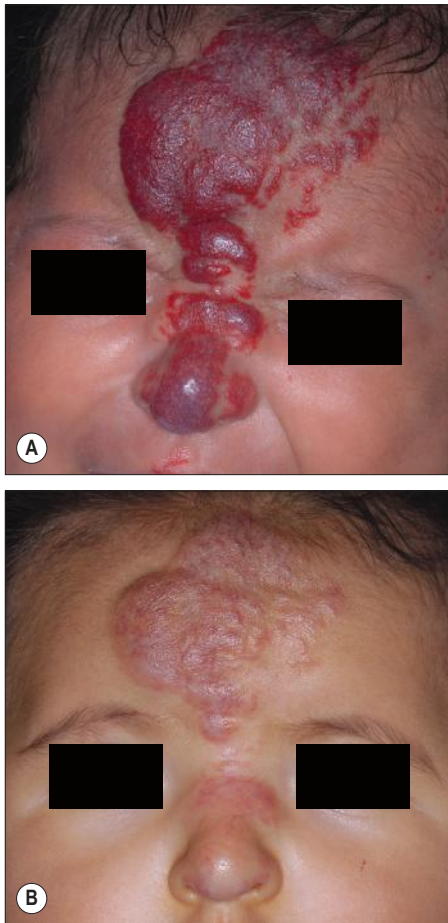


Figure 21.4 (A) This frontonasal (S4) and lower lip (S3) segmental hemangioma grew significantly by 7 weeks of age. (B) After 6 months of therapy with propranolol there was a significant decrease in color intensity and bulk, leaving residual atrophic skin changes that were most prominent in areas that corresponded to most exophytic portions of the hemangioma.

that are large, segmental, or those with a significant deep component growing much longer, even beyond the age of 1 year.^{17,18} Most hemangiomas establish the boundaries of their anatomic territory relatively early, growing only in volume thereafter. Superficial hemangiomas initially have a bright red color early in proliferation. Both combined and deep hemangiomas may feel tense, and fluctuations in size and volume may be noted with crying or activity. The earliest signs of involution include a change in color from bright red to a violaceous gray, usually beginning in the center of the hemangioma. The deeper portion also regresses, but this is often not as apparent clinically. Parents may note less fluctuation in hemangioma size during crying and less tumor firmness.⁶ The warmth of the hemangioma diminishes with time. Some resolve leaving normal or nearly normal skin, whereas others resolve with residua of variable cosmetic significance (Fig. 21.4). Involved hemangiomas often show residual telangiectasia, pallor or a yellowish color, fibrofatty tissue deposition, and atrophy (Fig. 21.5). Several studies have shown that completion of involution occurs at a rate of approximately 10% per year, with 30% completing involution at 3 years, 50% at 5 years, etc.^{4,19} Although not specifically mentioned in these studies, it seems that small hemangiomas generally involute sooner than very large, bulky ones.



Figure 21.5 Involved hemangioma. This 4 year-old child has permanent skin changes after hemangioma involution, with atrophic, inelastic skin (anetoderma) as well as residual telangiectasias centrally.



Figure 21.6 Infantile hemangioma with minimal or arrested growth (IH-MAG). A 3-month-old female with reticulated vascular plaque on the lower leg with small pinpoint bright red proliferative papules arising on less than 25% of its surface area.

Less commonly, infantile hemangiomas display a more atypical growth pattern characterized by little, if any postnatal growth. These hemangiomas have been variously called infantile hemangiomas with minimal or arrested growth (IH-MAG), abortive hemangiomas, or reticular hemangiomas.^{20,21} IH-MAG present as telangiectatic patches that have minimal superficial proliferation, often manifested as 1–3 mm red papules at the periphery of the lesion and have a predilection for the lower extremities (Fig. 21.6).²² They may have violaceous to green ectatic vessels underlying the finer telangiectasias. The small proliferative vascular papules involute within the first few years of life but the ectatic vessels can be persistent. The vessels of IH-MAG stain positively for GLUT-1, similar to classic infantile hemangiomas.

Ulceration is the most common complication of infantile hemangiomas, occurring in approximately 10–15%, most often during the rapid growth phase. The risk is much higher (approx. 50%) for hemangiomas involving the lip and perineum.²³ When



Figure 21.7 Hemangioma on the scalp with painful ulceration. Ulceration is the most common complication of infantile hemangiomas.

BOX 21.1 INDICATIONS FOR WORKUP FOR ASSOCIATED EXTRACUTANEOUS ANOMALIES

- Large facial hemangiomas >5 cm (PHACE syndrome)
- Lumbosacral hemangiomas >2.5 cm (spinal dysraphism)
- Large lower trunk or lower extremity hemangiomas (PELVIS syndrome)
- More than 5 cutaneous hemangiomas (extra-cutaneous hemangiomas, especially hepatic)
- Beard distribution hemangiomas (airway hemangioma)

the ulceration heals, there is virtually always residual atrophy or scarring. Bleeding may occur, but profuse bleeding is surprisingly rare, occurring mainly with deeply ulcerated hemangiomas or those located on the scalp (Fig. 21.7). Superimposed bacterial infection most commonly with *Staphylococcus aureus* or *Pseudomonas* species may develop and may impede healing, but it is uncommon. Recurrent ulceration may complicate hemangiomas located in the perineum.

The Kasabach–Merritt phenomenon (KMP) was originally believed to be a complication of large hemangiomas, but studies have proven that KMP is a complication of other vascular tumors, including kaposiform hemangioendothelioma and tufted angioma, rather than infantile hemangiomas (see below).

High-risk hemangiomas. Although the vast majority of hemangiomas are not worrisome and do not necessitate treatment, it is important to recognize the subsets of hemangiomas that are at highest risk for causing permanent disfigurement, impairing vital functions including vision and feeding, and that may be associated with visceral hemangiomatosis or internal anomalies (Box 21.1).

Locations associated with high risk for disfigurement. The most common reason infants with hemangiomas receive treatment is the potential risk for disfigurement (Fig. 21.8).⁵ Hemangiomas involving the central face may distort important anatomic landmarks and have a significant impact on future cosmesis. Although exophytic lesions on the medial cheek do not impair vital functions, they are often distressing because of their conspicuous locations and may benefit from more aggressive medical therapies. Distortion of the lip contour can occur

even with small hemangiomas because of the disruption of the vermillion border or loss of the curvature of the philtrum. Mixed hemangiomas located on the nasal tip distort the underlying cartilage and leave residual bulk. Surgical repair is often necessary to correct the ‘Cyrano nose’ deformity that can result in splaying of the nasal cartilage. Ulceration involving the columella can lead to destruction of the nasal septum. Hemangiomas on the pinna may ulcerate and become secondarily infected, contributing to structural deformity of the involved ear.

Periorbital hemangiomas. Growth of periorbital and lid hemangiomas may cause visual impairment principally by deformation of the cornea, creating refractive errors or less commonly by obstructing the visual axis. If severe or persistent, this can lead to amblyopia. Large and/or segmental hemangiomas in the periocular area have the greatest risk of these complications, but even small lesions may pose a threat to normal visual development, with astigmatism being the most common sight-threatening ocular complication.^{24,25} Proliferation of retrolbulbar lesions may lead to proptosis, strabismus, and visual compromise.²⁶

Large cervicofacial hemangiomas and PHACE syndrome. Large cervicofacial hemangiomas may impair vital functions, distort normal anatomy, or lead to congestive heart failure as they proliferate. These problematic hemangiomas are more common in females than males at a ratio approaching 9:1 in some series.²⁷ The term PHACE syndrome refers to the association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities (Box 21.2). The term PHACE(S) is sometimes used when associated sternal anomalies or a supraumbilical raphe are present. Although the exact incidence of PHACE is unknown, it may be more common than Sturge–Weber syndrome.²⁷ In 2009, a multidisciplinary panel of experts published diagnostic criteria for ‘definite’ and ‘possible’ PHACE using specific major and minor criteria.²⁸ A multicenter prospective study of 108 infants with facial hemangiomas measuring 22 cm² or larger, found that when applying published diagnostic criteria for PHACE, 31% had PHACE and 90% of affected infants had more than one extracutaneous finding. The most common extracutaneous manifestation in PHACE is anomalous cerebrovasculature, with the highest incidence seen in infants with upper face hemangiomas (S1, frontotemporal or S4, frontonasal) (Figs 21.4, 21.9).²⁹

Central nervous system (CNS) anomalies include both structural malformations of the brain and anomalous vasculature of the head and neck, both of which are typically ipsilateral to the cutaneous hemangioma.³⁰ Structural CNS malformations include the Dandy–Walker malformation and other posterior fossa anomalies, such as arachnoid cyst, enlarged fourth ventricle, enlarged cisterna magna, and cerebellar or vermian hypoplasia.^{31–33} Other CNS anomalies have been reported, including cerebral atrophy, gray matter heterotopia, pituitary abnormalities, and absent corpus callosum. Macrocephaly, ophthalmologic abnormalities, hypotonia, seizures, and psychomotor retardation may be a presenting sign of an underlying structural malformation. Cerebrovascular abnormalities often involve the ipsilateral internal carotid artery and its branches, though other vessels can be involved.³⁰ Dysgenesis of the vessel, including looping, elongation, ectasia, kinking, and focal or fusiform aneurysmal enlargement of the vessel, is most frequently noted.³⁰ Less commonly, vessels can have an anomalous course and/or origin, display narrowing or be completely

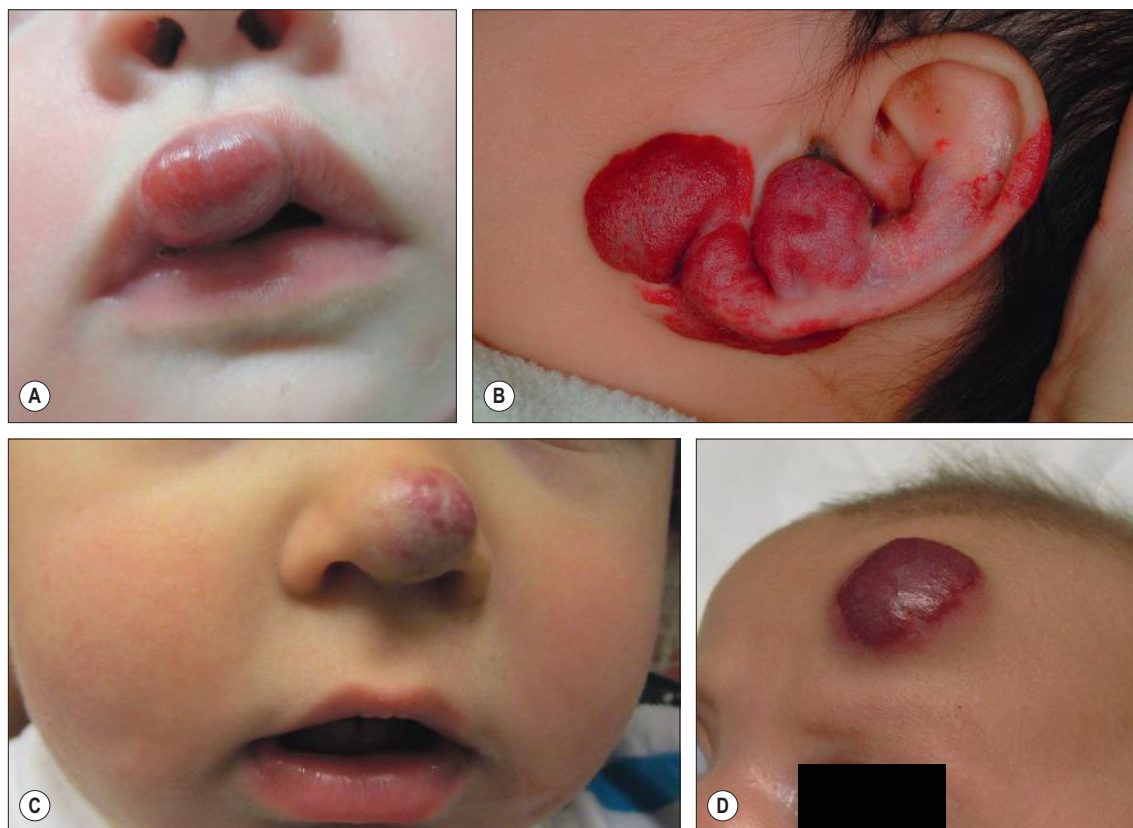


Figure 21.8 Hemangioma locations associated with a high risk for disfigurement including the (A) lip, (B) ear, (C) nose, and (D) forehead.

BOX 21.2 PROPOSED EVALUATION FOR PHACE SYNDROME IN INFANTS WITH FACIAL HEMANGIOMA >5 CM

- MRI with contrast and MRA of head and neck for cerebrovascular and structural anomalies
- Echocardiogram to assess for coarctation or structural cardiac anomalies
- Ophthalmologic examination for retinal and other ocular abnormalities
- Careful examination for ventral midline defects
- Other studies, depending on signs and symptoms, as indicated (i.e., endocrine evaluation)



Figure 21.9 Segmental frontotemporal (S1) hemangioma mimicking a capillary malformation. Although the location resembles a V1 distribution, there is no risk of Sturge-Weber syndrome. However, the patient is at risk for the cerebrovascular, cardiac, and eye anomalies associated with PHACE syndrome.

absent.³⁰ Rarely, patients with intracranial anomalous vessels may demonstrate progressive occlusive arterial changes and cerebral infarction.³⁴ Stroke is a rare complication of PHACE and may be more common in patients with aplasia, hypoplasia or occlusion of a major cerebral artery.³⁵ Other neurologic sequelae of PHACE may include seizures, migraine-like headaches, and developmental delay, including most commonly language and gross motor abilities.³⁶

Cardiac abnormalities, seen in two-thirds of infants with PHACE, usually manifest as unusual forms of aortic arch coarctation, primarily involving long segment narrowing of the

transverse aorta often associated with adjacent dilatation or aneurysms.^{29,37,38} Less frequently, structural anomalies of the heart may be seen, including atrial and ventricular septal defects.²⁸

Less common manifestations include ocular, midline anomalies and hearing loss of the affected ear.³⁹ Ocular findings may include persistent fetal vasculature, retinal vascular anomalies, optic nerve hypoplasia, morning glory deformity, peripapillary staphyloma and coloboma, with other less specific anomalies noted more rarely. Midline defects such as partial or complete sternal agenesis and supraumbilical raphe may also occur.^{28,40}

Endocrine abnormalities, including pituitary dysfunction, thyroid dysfunction, and growth hormone deficiency have been reported in some patients with PHACE. A few infants with PHACE have been noted to have absent or lingual thyroid glands.^{41–43}

Lumbosacral hemangiomas and regional anomalies. Analogous to PHACE syndrome, segmental lumbosacral and perineal hemangiomas can be cutaneous signs of regional anomalies such as underlying structural malformations of the genitourinary, gastrointestinal, neurologic, and skeletal systems (Fig. 21.10).⁴⁴ The acronyms for this association include LUMBAR, PELVIS, and SACRAL syndromes.^{44–46} A prospective study of 41 lumbosacral hemangiomas >2.5 cm reported 35% had evidence of spinal dysraphism.⁴⁷ Tethered spinal cord, spinal lipomas and spinal hemangiomas are the most common underlying abnormalities.⁴⁸ Imperforate anus, rectosigmoid fistula, renal anomalies, abnormal external genitalia, lipomyelomeningocele, and bony deformities of the sacrum have been reported.^{44–46} Ulceration is associated with a higher risk of underlying anomalies.⁴⁷

Multifocal cutaneous and visceral hemangiomas. Multiple hemangiomas occur in approximately 10–25% of infants and are more common in premature infants than in term infants.⁴⁹ Cutaneous lesions may range in size from a few millimeters to more than several centimeters in diameter. The presence of five or more cutaneous hemangiomas is a known risk factor for

extracutaneous hemangiomas, mainly hepatic hemangiomas. Rarely, other organs such as the gastrointestinal tract, lungs, CNS, oral mucosa, and eyes may be affected. Screening ultrasound of the liver is recommended for young infants with five or more cutaneous hemangiomas.⁵⁰ Serial radiologic evaluation of the liver, especially screening abdominal ultrasound, with further evaluation with CT or MRI, may be necessary to follow progression of visceral lesions. Hepatic hemangiomas (HH) may be solitary or multiple. A classification for hepatic hemangiomas has been proposed, including solitary, multifocal, and diffuse HH.⁵¹ Solitary HH in the absence of cutaneous hemangiomas – particularly if detected in utero – are usually GLUT1 negative, regress rapidly, and most likely represent a form of vascular tumor in the liver similar to rapidly involuting congenital hemangioma (RICH) rather than true infantile hemangioma (see below). Multifocal hepatic lesions usually occur in the setting of multiple small skin hemangiomas. They may be completely asymptomatic without the need for treatment, but if they have arteriovenous shunts, they may require liver embolization and/or medical therapy to manage congestive heart failure, as well as hemangioma-specific therapy (such as beta-blockers). Hepatic hemangiomas associated with an arteriovenous, arterioportal shunt or portovenous fistula are associated with greater morbidity.⁵¹ Diffuse liver hemangiomas cause massive hepatomegaly, abdominal compartment syndrome, and are associated with hypothyroidism (see below). They have a high rate of mortality and require aggressive medical therapy, and even consideration of liver transplantation.

Consumptive hypothyroidism may occur in association with hepatic hemangiomatosis due to the deactivation of thyroxine by a type 3 iodothyronine deiodinase produced by the hemangioma.^{52–54} This form of hypothyroidism can be detected by the presence of markedly elevated TSH and low T₃, T₄ levels may be normal or low. Neonatal screening for hypothyroidism is inadequate to assess for this complication, as the most active phase of hemangioma proliferation typically occurs after this period. In some cases, this consumptive form of hypothyroidism may require large doses of thyroid hormone replacement given intravenously. The hypothyroidism typically resolves as the hemangioma regresses, but may have already caused significant morbidity if not detected promptly. Type 3 iodothyronine deiodinase activity has also been found in association with large cutaneous hemangiomas, therefore thyroid function tests should also be considered in patients with large cutaneous hemangiomas.⁵²

Cutaneous hemangiomas associated with airway hemangiomas. Infantile hemangiomas of the airway are most commonly seen in the subglottis and can occur with or without cutaneous hemangiomas. Hemangiomas in the ‘beard distribution’ involving the skin overlying the mandible, chin, and neck, have a high risk of concomitant airway involvement (Fig. 21.11). There is a striking female predilection of 6–7:1 for ‘beard’ hemangiomas.⁵⁵ Though hemangiomas in the mandibular region are most common, other hemangioma patterns that have been associated with airway hemangiomas include unilateral multi-segment and hemifacial hemangiomas.^{56,57} Affected infants typically present within the first few weeks of life with an increasing degree of noisy breathing, stridor, hoarse cry, or other signs of airway obstruction. Having an airway hemangioma together with one or more large facial hemangiomas confers a greater than expected incidence of PHACE – possibly as high as 47%.⁵⁷



Figure 21.10 LUMBAR-PELVIS-SACRAL syndrome. Hemangioma in association with a cutaneous lipoma and spinal dysraphism. This infant had a telangiectatic IH of the lumbosacral skin and buttocks with recurrent ulceration. The lack of significant proliferation, peripheral halo and telangiectasias are consistent with an IH-MAG. MRI revealed an underlying tethered spinal cord and spinal lipoma.



Figure 21.11 Mandibular (S3) hemangioma associated with subglottic hemangioma.

PATHOGENESIS

Infantile hemangiomas are believed to represent localized areas of abnormal vascular growth, and several hypotheses have been proposed to explain their pathogenesis. These include endothelial cell defects, a placental origin, extrinsic abnormalities in neighboring cells and exposure to vascular growth stimulators. IH was long thought to be a disease of aberrant angiogenesis, however more recent research supports the idea that it may also represent a disorder of vasculogenesis, that is the formation of new blood vessels *de novo*, rather than sprouting from pre-existing cells. While some evidence supports many of the proposed hypotheses, no unifying paradigm has emerged: it is likely that the pathogenesis is multifactorial with many mechanisms contributing to their development, proliferation and involution.^{58–60}

Some evidence suggests that hemangioma endothelial cells represent a clonal expansion of cells due to a somatic mutation in genes that play a significant role in vascular growth or vascular regulatory pathways. Mutations in several genes involved in the VEGF signaling pathway (VEGF receptors), Tie-2 and Dusp-5 have been noted supporting this hypothesis, but their exact role in hemangioma pathogenesis is not clear.^{61–63} Initial analysis of several pedigrees of familial hemangiomas revealed a linkage to chromosome 5q.⁶² Subsequent analysis of sporadic hemangiomas demonstrated loss of heterozygosity of 5q, further supporting the possibility that somatic mutations play a role in hemangioma formation.⁶⁴

Infantile hemangiomas share unique immunohistochemical markers with human placenta microvasculature. North and coworkers reported that glucose transporter protein-1 (GLUT-1) is expressed by infantile hemangiomas during all phases of their development (proliferating, involuting, and involuted), distinguishing infantile hemangiomas from vascular malformations and other vascular tumors.⁶⁵ Other placenta-associated vascular antigens, including merosin, FcγRII and Lewis Y antigen, are also present in hemangiomas and absent in microvessels of normal skin.⁶⁶ In addition, studies using DNA microarray techniques have revealed that the gene expression profiles of hemangiomas and placenta vascular endothelium are remarkably similar.⁶⁷ While it is speculated that hemangiomas may arise from embolized placental cells or angioblasts that

abnormally differentiate toward a placental phenotype, this is challenged by the finding of negative placental trophoblastic markers in immunochemical analysis of hemangiomas.⁶⁸

Multiple factors regulate the proliferation and involution of hemangiomas. During proliferation, hemangiomas demonstrate proliferating cell nuclear antigen (PCNA), as well as increased levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).^{69–71} The VEGF signaling pathway is likely one of the more important mechanisms contributing to hemangioma proliferation.⁷² Angiogenesis mediators, including monocyte chemoattractant protein-1 and the adhesion molecules E-selectin and ICAM-3, are also expressed at high levels.^{73–76} Proteins involved in extracellular matrix remodeling are expressed during the proliferating phase.^{59,69,77} Increased levels of urinary matrix metalloproteinase (MMP) proteins are noted in proliferating infantile hemangiomas, suggesting a role in extracellular matrix remodeling, and the expression of lymphatic endothelial hyaluronan receptor-1 (LYVE-1) in proliferating hemangiomas may explain the rapid growth.^{78,79} Local factors are also believed to play a significant role in hemangioma proliferation. Investigators have noted that hemangioma growth correlates with hyperplasia of the overlying epidermis, with these tissues elaborating angiogenic factors (e.g., VEGF, bFGF). Moreover, these tissues lacked expression of the angiogenesis inhibitor interferon (IFN)-β.⁸⁰ Indoleamine 2,3-dioxygenase (IDO) enzyme activity may play a role in the transition from proliferation to involution.⁸¹

During involution, the levels of angiogenic factors found during proliferation decrease, whereas levels of the angiogenesis inhibitor TIMP-1 (tissue inhibitor of metalloproteinase -1) increase.^{69,75,76} Interferon-regulated genes are upregulated during involution.^{69,82} Factors that promote apoptosis increase during involution, whereas inhibitors of apoptosis are upregulated during proliferation.^{83–85} In addition, loss of Dusp-5 function increases apoptosis in human umbilical vein endothelial cells causing speculation for its role in hemangioma involution.^{72,86}

DIAGNOSIS

Most infantile hemangiomas can be diagnosed on the basis of history and clinical appearance. The differential diagnosis includes other vascular and nonvascular tumors that are discussed elsewhere. Where history and physical examination are not helpful, further studies such as imaging or even biopsy may be necessary to confirm the diagnosis. Doppler ultrasound and MRI are most helpful in confirming the diagnosis of hemangioma. Doppler studies demonstrate high-flow lesions. T₁-weighted MRI sequences demonstrate flow voids as a result of high-flow vessels and enhancement on T₂-weighted sequences.^{87–89}

HISTOPATHOLOGY

If there is significant diagnostic uncertainty, a biopsy and GLUT-1 staining may be necessary to exclude other soft tissue tumors or vascular malformations. Early in the proliferating stage this tumor consists predominantly of a mass of endothelial cells. Lumina, lined by normal-appearing endothelial cells, become evident somewhat later in the late proliferative phase. PAS stains reveal a thickened basement membrane. Mast cells are increased within proliferating hemangiomas compared to

TABLE 21.1 Hemangioma evaluation and management

Hemangioma presentation	Association or complication	Evaluation and treatment
Facial segmental hemangiomas/facial hemangioma >5 cm	PHACE syndrome	MRI/MRA of brain and neck, echocardiogram, ophthalmology evaluation, and consider topical and/or systemic therapy
Periocular hemangioma	Ocular complications	Ophthalmology evaluation and consider topical and/or systemic therapy
Lumbosacral hemangioma	Spinal dysraphism, intraspinal hemangioma, lipoma	MRI of spine or ultrasound spine if neonate, neurosurgical intervention if indicated, consider topical and/or systemic therapy
Perineal segmental hemangioma	Spinal dysraphism and genitourinary anomalies (PELVIS syndrome)	MRI of lumbar spine and pelvis, urological and neurosurgical intervention if indicated, consider topical and/or systemic therapy
Ulceration	Pain, bleeding, scarring	See Box 21.6
Central facial or other hemangiomas distorting normal anatomy	Disfigurement from skin and/or cartilage destruction and deformation	Consider topical and/or systemic therapy
Airway hemangiomas	Respiratory distress	Otolaryngology evaluation and/or MRI of neck, systemic therapy
Multifocal hemangiomas (>5)	Hepatic hemangiomas	Hepatic ultrasound and systemic treatment if symptomatic

normal tissue. As hemangiomas mature, they show lobules of endothelial channels separated by fibrous septa. Actin-positive smooth muscle cells are deposited around the vessels. Fat cells may be prominent in some involuted hemangiomas. Immunohistochemical analysis with GLUT-1 can be used to confirm the diagnosis of infantile hemangioma.

DIFFERENTIAL DIAGNOSIS

Deep hemangiomas may be particularly difficult to differentiate from other tumors and malformations (Box 21.3).^{90,91} Infantile myofibromatosis may mimic vascular tumors but is firmer to palpation and has distinct histopathologic features. Infantile fibrosarcoma, a rare tumor that is sometimes congenital, may resemble a deep hemangioma or lymphatic malformation. Rhabdomyosarcoma is the most common sarcoma of early childhood and may present in newborns as a rapidly enlarging red cutaneous mass, usually involving the head and neck, that may be difficult to differentiate from a deep hemangioma. Other benign and malignant tumors that may resemble hemangiomas include adrenal carcinoma, spindle and epithelioid nevi, hemangiopericytoma, dermatofibrosarcoma protuberans, lipoblastoma, neuroblastoma, and nasal glioma. Congenital Langerhans' cell histiocytosis, multifocal lymphangioendotheliomatosis and disseminated pyogenic granulomas may mimic diffuse neonatal hemangiomatosis. Developmental anomalies such as encephaloceles, dermoid cysts, meningoceles, and teratomas may all be mistaken for deep hemangiomas.

MANAGEMENT

Perhaps the greatest challenge in managing hemangiomas in infancy is the identification of those lesions that need treatment. Because of widely divergent sizes, location(s), and the rapid changes that can occur in early infancy, it may be difficult to predict prognosis at the time of initial evaluation. Frequent assessments during the first few weeks to months of life may be needed, particularly if high-risk features are present. The major goals of management are the prevention and treatment of life-threatening or function-threatening complications of the hemangioma as well as the prevention of permanent disfigurement

that may have a long-term social and psychosocial impact on the patient and family (Table 21.1).⁹²

There are a number of treatments employed for infantile hemangiomas, although there is currently no treatment specifically FDA-approved for this indication. There are topical and systemic therapies that target hemangioma proliferation as well as adjunctive therapies that address hemangioma-related complications or the appearance of hemangioma residua after involution. The potential benefits of any form of treatment should be carefully weighed against the associated risks.

Several clinical features are important to consider when choosing treatment. It is important to consider not only anatomic location, but also the size, type, and pattern of the hemangioma and whether the hemangioma is actively proliferating. The following sections describe some of the treatment methods that have been employed.

Active non-intervention. This term refers to the active observation and anticipatory guidance that can be given to parents, even if no specific therapy is instituted. Parents may feel significant distress as they await spontaneous involution and may react with disbelief, fear, and mourning. Some feel a degree of social stigmatization and many are accused of child abuse, either jokingly or in earnest. Parent-child interactions may be adversely affected.⁹² A careful discussion of the natural history of hemangiomas, with photographic examples to demonstrate natural involution, as well as a thorough discussion of therapeutic options, may help allay parental fears. Frequent visits, measurements, and photographs during the proliferating phase are recommended, and as the hemangioma begins to involute, visits can become less frequent. Acknowledgment of the intrusive and unsolicited questions and advice parents may receive can also be helpful.

Local and topical treatment. For superficial hemangiomas that have not yet become large or exophytic, topical treatment may be beneficial, including topical steroids, beta-blockers, and imiquimod. Initially described for the treatment of superficial, periocular hemangiomas, ultrapotent topical steroids such as clobetasol may decrease hemangioma size as well as reduce the thickness and color intensity of the hemangioma.^{93–95} Steroid-induced cataracts and increased intraocular pressure are theoretical risks and therefore patients using potent topical steroids

BOX 21.3 CONDITIONS MASQUERADING AS INFANTILE HEMANGIOMAS

VASCULAR TUMORS AND MALFORMATIONS:

- Congenital hemangioma (rapidly involuting and non-involuting)^a
- Tufted angioma^a
- Kaposiform hemangioendothelioma^a
- Spindle cell hemangioma (Maffucci syndrome)^a
- Congenital eccrine angiomatous hamartoma
- Pyogenic granuloma^a
- Capillary malformation^a
- Venous malformation^a
- Glomuvenous malformation^a
- Lymphatic malformation
- Combined vascular malformation (Klippel–Trenaunay syndrome)
- Verrucous ‘hemangioma’ and angiokeratoma
- Arteriovenous malformation
- Hereditary hemorrhagic telangiectasia^a

OTHER BENIGN TUMORS AND DEVELOPMENTAL ANOMALIES:

- Juvenile xanthogranuloma^a
- Pilomatricoma^a
- Infantile myofibromatosis^a/infantile hemangiopericytoma
- Solitary reticulohistiocytoma
- Lipoblastoma
- Sacral lipoma
- Encephalocele/meningocele
- Heterotopic brain tissue
- Dermoid cyst
- Plexiform neurofibroma^a
- Spitz nevus

MALIGNANT TUMORS:

- Dermatofibrosarcoma protuberans
- Giant cell fibroblastoma
- Infantile fibrosarcoma
- Rhabdomyosarcoma^a
- Lymphoblastic lymphoma

MULTIFOCAL DISEASES:

- Multifocal lymphangioendotheliomatosis
- Blue rubber bleb nevus syndrome
- Capillary malformation-AVM
- Langerhans’ cell histiocytosis
- Primary or metastatic neuroblastoma
- Congenital leukemia cutis
- Peripheral primitive neuroectodermal tumor
- Adrenocortical carcinoma

^aCan be multifocal.

in the periocular area should have periodic ophthalmologic exams. Percutaneous absorption and hypothalamic-pituitary axis suppression may occur but the true risk for systemic absorption is unknown.

Timolol is a nonselective beta-adrenergic receptor inhibitor originally formulated for ophthalmologic use (0.25–0.5% solution or gel-forming solution) and has increasingly been reported as an alternative to topical steroids for superficial hemangiomas and some small mixed-type hemangiomas.⁹⁶ Although numerous cases have been reported, variability with regards to dose, frequency and vehicle exist and large clinical trials are still needed to elucidate its optimal use. Ophthalmologic doses (1–2 drops BID) have commonly been applied to avoid increasing the risk of systemic absorption. Timolol, when used intraocularly for glaucoma, is rarely associated with respiratory complications including bronchospasm.⁹⁷ The gel-forming solution may have lower systemic absorption compared to solution formulations of timolol and thus may be preferable to the standard solution vehicle.^{98–100} Importantly, topical treatment is not appropriate for periocular lesions that cause visual axis compromise or that are at risk for inducing significant astigmatism and amblyopia, where systemic treatment is more appropriate.

There are a few case reports of treating infantile hemangioma with the topical immunomodulator 5% imiquimod cream.^{101–103} This cream is approved for the treatment of genital warts, actinic keratoses and superficial BCC in adults. Further studies are needed to determine the safety and efficacy of this therapy in infants. Crusting or ulceration has been reported as a side-effect of topical treatment in some cases.

Intralesional corticosteroids. Intralesional steroid treatment may be useful in the treatment of small, localized hemangiomas in problematic locations such as the lips, tip of the nose, ear, or face. The frequency of injections is governed by clinical response: generally 1–3 treatments at 4–6-week intervals are needed. The dose of triamcinolone should not exceed 1–3 mg/kg per treatment session. Intralesional injection of hemangiomas on the eyelid with long-acting corticosteroid preparations may be complicated by occlusion of the central retinal or ophthalmic arteries, which may cause blindness.¹⁰⁴ Other complications associated with intralesional treatment in this area include intraocular deposits, eyelid necrosis, and scleroderma-like linear atrophy of the skin. Therefore, caution is advised when using intralesional steroids in the periocular region.¹⁰⁵ HPA axis suppression can occur in infants receiving large doses intralesionally.¹⁰⁶

Pulsed dye laser. The flashlamp-pumped pulsed dye laser (PDL) has been used to treat hemangiomas. Superficial lesions appear to respond best to this treatment.^{107–109} Hemangiomas with a deeper dermal component may show lightening of the superficial erythematous portion, but treatment does not affect the deeper portion. Early laser treatment and its impact on future hemangioma growth is controversial. Multiple treatment sessions over several months may be needed to treat superficial hemangiomas. Treatment appears to be relatively well tolerated, but the risk of scarring appears to be higher than when similarly aged infants with port-wine stains are treated, particularly for large hemangiomas in a rapidly proliferative state. A randomized controlled study of PDL for early hemangiomas failed to show substantial benefits at 1 year of age, but this study has been criticized by some because it used a type of PDL without more recent improvements, such as a cooling spray to spare epidermal injury.¹¹⁰ Side-effects include transient pigmentary alteration

and atrophic scarring.¹¹⁰ Severe ulceration and scarring have been reported, especially when treating segmental hemangiomas in the proliferative phase, although these observations were made using older laser technology and with treatment fluencies higher than now recommended.¹¹¹

The pulsed dye laser is an effective treatment for residual telangiectasia in involuted hemangiomas, and may also be effective for ulcerated hemangiomas. Some patients who fail to respond to topical treatment for ulceration respond with healing of the ulceration and subjective reduction of pain after laser treatment.^{112,113} Other laser light sources, including the argon and Nd:YAG lasers, have been used to treat hemangiomas in earlier series, but are associated with higher risks of ulceration and scarring.

Systemic therapy. Although systemic corticosteroids had been the mainstay of systemic treatment, more recently, beta-blockers have become first-line treatment for complicated IH. Propranolol is a nonselective beta-adrenergic antagonist that inhibits both beta-1 and beta-2 adrenoreceptors. In 2008, Léauté-Labrèze and colleagues reported the serendipitous discovery that propranolol had efficacy for infantile hemangioma treatment.¹¹⁴ Since that initial report, numerous case series have supported propranolol use both in the proliferative phase (Fig. 21.12), and – unlike systemic steroids – for older children with hemangiomas that have plateaued or partially involuted.^{115–117} Airway hemangiomas and hepatic hemangiomas have similarly been successfully treated with systemic propranolol alone or in combination with systemic steroids.¹¹⁸

Although the exact mechanism by which propranolol works for infantile hemangiomas has not yet been elucidated, its vasoconstrictive effects on vascular smooth muscle are hypothesized to be responsible for the color changes and softening of hemangiomas often observed within in the first few days of treatment. In vitro, propranolol has been shown to decrease levels of vascular endothelial growth factor (VEGF), an important mediator in hemangioma proliferation.¹¹⁹ Propranolol may also induce apoptosis of endothelial cells and decrease the VEGF angiogenic effects.¹²⁰

Because larger clinical trials are still in progress, use of propranolol is currently based on collective published experience and proposed consensus recommendations (Box 21.4).¹²¹ Propranolol is most commonly administered in initial oral doses of 0.5–1 mg/kg per day divided into twice or three times daily dosing with gradual titration over several weeks to achieve a target dose of 1–2 mg/kg per day in divided doses. A recent study has shown that doses of 3 mg/kg per day are also highly effective and well-tolerated, though some authors reserve its use for refractory cases. Before initiating treatment, evaluation of cardiovascular status includes exclusion of pre-existing heart block by a thorough cardiac exam and/or electrocardiogram, confirmation of normal vital signs, and formulation of a plan for monitoring vitals during the treatment period should be made.¹²¹ A history of bronchospasm or restrictive airway disease should be elicited and may be a relative contraindication to therapy. Recent guidelines for propranolol administration advocate caution with use in premature infants, infants under 8 weeks of age, and those with coexisting cerebrovascular or aortic anomalies.¹²¹ In these more vulnerable groups, consideration for inpatient observation during initiation is reasonable.¹²¹

Potential adverse effects of propranolol include hypotension, bradycardia, hypoglycemia, diarrhea, and sleep disturbance



Figure 21.12 Response to propranolol therapy. (A) A 10-week-old infant with ulcerated focal hemangioma of the left cheek. (B) The same infant after 2 weeks of propranolol therapy. The ulcer healed leaving a grayish-white scar centrally, and hemangioma bulk decreased. (C) An infant with a periocular hemangioma before therapy with propranolol. (D) After 3 months of propranolol.

BOX 21.4 PROPRANOLOL ADMINISTRATION

- History and physical exam for normal cardiovascular and pulmonary health (include HR, BP and pulmonary auscultation)
- Consider ECG or cardiology consultations to exclude heart block or arrhythmia
- Inpatient initiation for infants <8 weeks of age, 8 weeks adjusted gestational age, or infants with comorbidity
- Starting dose of propranolol of 1 mg/kg per day divided TID
- HR and BP monitoring at intervals (consider 1–2 h) after first dose as inpatient or in a clinic setting
- Dose escalation as needed for clinical response by increments of 0.5 mg/kg per day after an appropriate interval, up to 2–3 mg/kg per day
- HR and BP with dose escalation and routine follow-up exams

HR, heart rate; BP, blood pressure; ECG, electrocardiogram.

BOX 21.5 POTENTIAL ADVERSE EFFECTS OF SYSTEMIC PROPRANOLOL USED FOR TREATING HEMANGIOMAS

- Hypoglycemia
- Hypotension
- Pulmonary symptoms (wheezing/bronchoconstriction, pulmonary obstruction, apneic episode)
- Bradycardia
- Nightmares and other sleep disturbance
- Somnolence
- Extremity changes (cold or blue)
- Diarrhea
- GI upset
- Hyperkalemia
- Dental caries

(Box 21.5). In patients treated for infantile hemangioma, only rarely has symptomatic hypotension or bradycardia occurred. Perhaps more concerning is hypoglycemia that has been reported in patients treated for infantile hemangioma who had recent illness or prolonged fasting.¹²² Of note, children as old as 18 months have been reported to have symptomatic hypoglycemia during propranolol therapy.¹²² Regular feeding is suggested with avoidance of prolonged fasting. Long-term steroid

administration with the addition of propranolol therapy has been reported to induce hypoglycemia possibly due to associated adrenal insufficiency that may compound hypoglycemia risk.¹²³ Propranolol should be stopped if a child is ill and not tolerated feeds, and can be restarted after illness resolves and routine feeding resumes.

The duration of propranolol therapy varies but is typically at least 6–12 months. Treatment should extend beyond the proliferative period, in order to try to avoid rebound growth with many patients requiring treatment until 12–15 months of age.

Deep hemangiomas tend to grow longer and have a higher relapse rate compared with other hemangiomas.¹²⁴ Although propranolol may be discontinued abruptly, tapering doses over several weeks may allow observation for potential early rebound in some patients.

In patients with large facial hemangiomas at risk for PHACE syndrome, imaging for significant cerebrovascular and aortic anomalies should be done prior to the initiation of propranolol, to assess the risk of potential complications if a hypotensive episode were to occur. Propranolol has been used successfully to treat patients with PHACE syndrome and the diagnosis of PHACE syndrome is not an absolute contraindication.¹²⁵ However, its administration in these patients should proceed with caution and in collaboration with a neurologist or cardiologist as appropriate.

Corticosteroid therapy. Systemic corticosteroids are also efficacious for hemangiomas, but have significant potential side-effects.¹²⁶ Prednisone or prednisolone at a dosage of 2–3 mg/kg per day is used during the proliferating phase to slow or halt the growth of the hemangioma, and some authors advocate even higher doses.¹²⁷ A systematic review of systemic corticosteroids used during the proliferating phase of infantile hemangioma¹²⁸ found that most infants responded to treatment with cessation of growth. Therapy is slowly tapered over several months. The duration of treatment depends on response to therapy and the amount of time the hemangioma remains in the proliferating period.

A review of 62 children treated with prednisone or prednisolone at an initial dose of 2–3 mg/kg per day tapered over a mean of 7.9 months showed a low incidence of serious side-effects.¹²⁹ Cushingoid facies, ‘personality changes,’ gastric irritation, and perineal and oral candidiasis are the most frequently reported short-term side-effects. Retardation of growth, including both height and weight, is also noted, with infants experiencing catch-up growth after cessation of therapy. Hypothalamopituitary–adrenal axis suppression is common, and the need to taper steroid doses prior to discontinuation is important. Hypertension is a potential complication of higher-dose therapy.¹³⁰ In addition, patients should be cautioned about the risk of immunocompromise and susceptibility to infection, and live-virus vaccines should be avoided during corticosteroid treatment. *Pneumocystis carinii* pneumonia has been reported in an infant receiving corticosteroid therapy for infantile hemangioma.¹³¹ There are recent reports of neurotoxicity occurring in very premature infants receiving corticosteroid therapy within the first few weeks of life (in an attempt to prevent chronic lung disease).¹³² This type of neurotoxicity has not been reported to date in term infants receiving systemic corticosteroids; however, further studies would be helpful to determine optimal treatment protocols and to assess for short- and long-term side-effects.

Other therapies. Recombinant interferon- α has been successful in the treatment of life-threatening hemangiomas that have failed to respond to corticosteroid therapy.^{133–135} Both interferon- α 2a and - α 2b have been used. The most common treatment regimen consists of a daily injection of 3 million U/m² as needed.¹³⁴ The response to therapy is variable, with some patients responding rapidly over the course of 3–6 months and others needing longer periods of treatment. Side-effects associated with treatment include fever, neutropenia, altered hepatic function chemistries, flu-like complaints, and agitation. Spastic diplegia, a side-effect reported in five of 26 infants receiving

interferon- α 2a for hemangiomas, is a particularly worrisome potential complication.¹³⁶ Although this has led some to recommend the use of the α 2b preparation, neurotoxicity has also been reported with this preparation. The risk of neurotoxicity after age one may be lower.¹³⁶ Neurodevelopmental status should be assessed at baseline, and monthly during and after treatment with interferon- α .

Vincristine has been used to treat corticosteroid-resistant hemangiomas and ‘vascular tumors’ as well as Kasabach–Merritt syndrome.¹³⁷ This chemotherapeutic agent is a vinca alkaloid that interferes with microtubule formation during mitosis by inhibiting tubulin. In vitro, it induces apoptosis of tumor and endothelial cells.¹³⁸ Peripheral neuropathy, constipation, jaw pain, anemia, and leukopenia are potential toxicities. Administration through a central venous catheter may be necessary, and the participation of a pediatric oncologist/hematologist is advised. It is usually effective, but studies are needed to determine the indications for its use, the incidence of adverse reactions, and the optimal dosage regimen.¹³⁹

Surgical excision. Surgical excision is usually reserved for involuted hemangiomas to remove residual fibrofatty tissue and redundant skin. Early excision is indicated for a small subset of hemangiomas. These include periorbital hemangiomas that fail to respond to pharmacologic therapy, or patients in which medical therapy is believed to pose a greater risk, painful chronically ulcerated hemangiomas that have failed more conservative treatment, some large nasal tip hemangiomas, and some pedunculated hemangiomas that will inevitably result in prominent fibrofatty residual tissue even after involution is complete.

Treatment of ulceration. Ulceration is the most common complication of infantile hemangioma and should be treated promptly (Box 21.6). All ulcerations leave some degree of scarring. Ulceration can also cause pain, which can be severe, particularly in perioral and perineal locations,¹⁴⁰ and medications to control pain, oral antibiotics, and other modalities such as pulsed dye laser may be necessary. There have also been reports

BOX 21.6 MANAGEMENT OF HEMANGIOMA ULCERATION

- Topical wound care. May include one or more of the following:
 - Sparing application of topical antibiotic, such as polymyxin B/bacitracin ointment, mupirocin or metronidazole gel
 - Liberal use of petrolatum or Aquaphor® to create an occlusive environment
 - Occlusive dressing such as:
 - Polyurethane film or ultrathin hydrocolloid dressing if able to adhere this to surrounding skin
 - Non-stick dressing with paper or linen tape
 - Vaseline®-impregnated gauze
 - When crust or eschar present, soak twice daily with warm water or dilute hydrogen peroxide
- Pain control with one or more of the following:
 - Acetaminophen with or without hydrocodone as needed
 - Sparing application of topical lidocaine periodically if pain is severe
- Bacterial culture if malodorous, purulent exudate, or other signs of infection
- Consider other modalities (pulsed dye laser, becaplermin gel, systemic corticosteroids, systemic propranolol, topical timolol, systemic antibiotics, excisional surgery), as indicated by the clinical situation

of improvement after the application of 0.01% becaplermin (recombinant platelet-derived growth factor),^{140,141} but becaplermin is approved for the treatment of diabetic ulcers in adults and not approved for use in children. Its mechanism of action includes the promotion of angiogenesis, which raises questions about its potential for stimulating growth and worsening of hemangiomas. Topical beta-blockers have been helpful in some cases but the systemic absorption through the ulcer bed is not known. Systemic therapy may be indicated in some patients with ulcerated hemangiomas, and excisional surgery may need to be considered when medical therapy fails.

Other vascular tumors

The more rare vascular tumors discussed in the following sections are recognized by their clinical and histopathologic features and immunohistochemical markers. Recognition may require a skilled pathologist who is familiar with these vascular lesions.

CONGENITAL HEMANGIOMAS

Hemangiomas that are fully formed tumors at birth and do not proliferate in postnatal life are distinct entities referred to as 'congenital hemangiomas'.^{142,143} There are two subtypes of congenital hemangiomas which are differentiated based on their natural history: the rapidly involuting congenital hemangioma (RICH) and the non-involuting congenital hemangioma (NICH).

Cutaneous findings

Both RICH and NICH are more common on the extremities or on the head and neck, vary in size from a few centimeters to 10–12 cm, and are often warm to palpation.^{142,144} They are usually solitary with rare cases of multifocal RICH reported.¹⁴⁵ The proliferating phase of both RICH and NICH occurs in utero with no further growth occurring after birth. Three clinical morphologies of RICH have been described: (1) a raised violaceous tumor with prominent peripheral vasculature; (2) a raised tumor with overlying coarse telangiectasias with skin blanching, often a peripheral halo of pallor; and (3) a pink to violaceous tumor with deeper infiltrative papules or nodules (Fig. 21.13A–D). The overlying skin may show hypertrichosis. Accelerated spontaneous involution starts in the first weeks of life,^{142,143} with regression by 14 months of age. After involution, atrophy, milia, telangiectasias and dilated veins may persist. Rarely, complete involution of RICH occurs in utero with atrophy at the site present at birth.¹⁴⁶

NICH may present as patches or large vascular tumors (Fig. 21.14). Enlarging draining veins are typical with both NICH morphologies. The lesions are usually less exophytic and less impressive in appearance than a RICH. They grow proportionately with the child and do not regress spontaneously. Some of these lesions clearly show arteriovenous microfistulas on Doppler examination, and these may develop increasing equatorial draining veins after years. They are often misdiagnosed in infancy as an infantile hemangioma, and the correct diagnosis is delayed until adolescence or adulthood, when they are excised, after having failed to involute. NICH may be painful in a minority of cases. Some cases of RICH involute only partially, and the residual tumor resembles NICH, supporting the concept that RICH and NICH may exist as a spectrum.¹⁴⁷

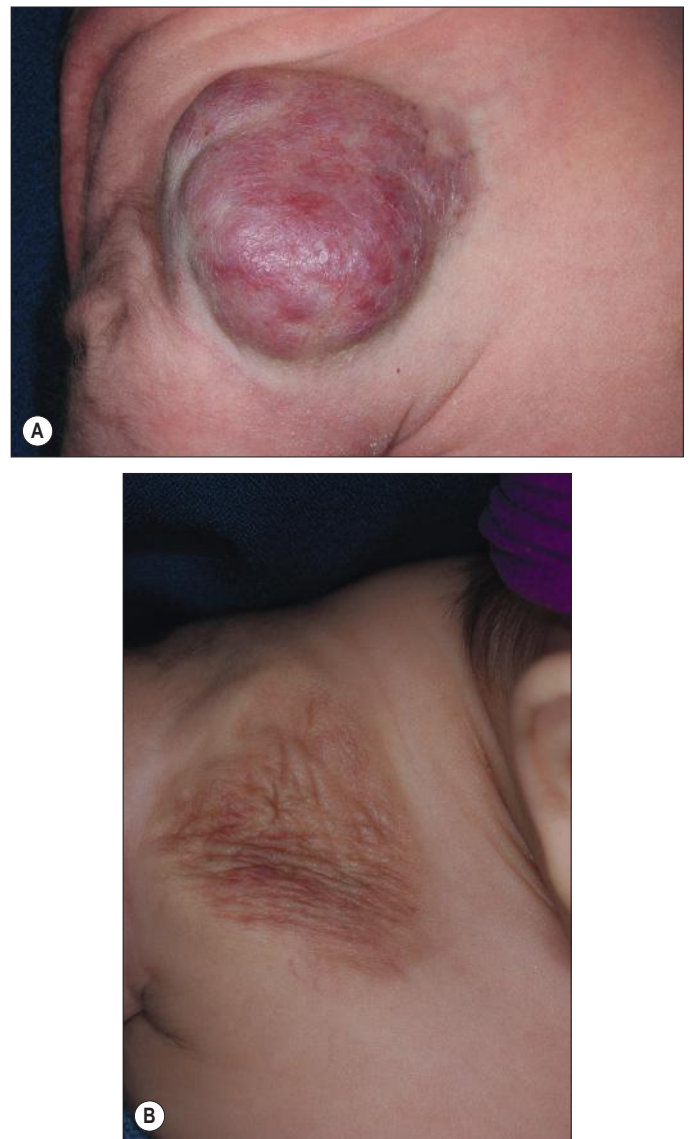


Figure 21.13 Rapidly involuting congenital hemangioma on the right upper shoulder at (A) 1 week of age and (B) 3 months of age. Rapid regression of the tumor has left redundant soft tissue changes.

Ulceration is a rare complication in a congenital hemangioma and is primarily reported with a RICH soon after birth. Ulceration is usually noted in the center of a lesion and may be preceded by a necrotic crust. Severe bleeding episodes have been reported in association with ulceration.^{148,149} Necrosis and ulceration are rarely reported with a NICH.

Extracutaneous findings

A RICH may also present as a solitary hepatic lesion, often in an otherwise healthy infant. Some of these infants experience thrombocytopenia and anemia and rarely congestive heart failure due to arteriovenous shunting. In severe cases, treatment may be warranted with surgery, embolization and rarely liver transplantation.^{150,151} Transient coagulopathy with thrombocytopenia has been reported to occur with a cutaneous RICH and can be confused with mild Kasabach–Merritt phenomenon. Rarely, more severe coagulopathy and congestive heart failure are seen with cutaneous lesions alone.^{152,153}



Figure 21.13 (C,D) Two examples of rapidly-involuting congenital hemangioma (RICH), a condition that usually involutes rapidly in the first year of life.

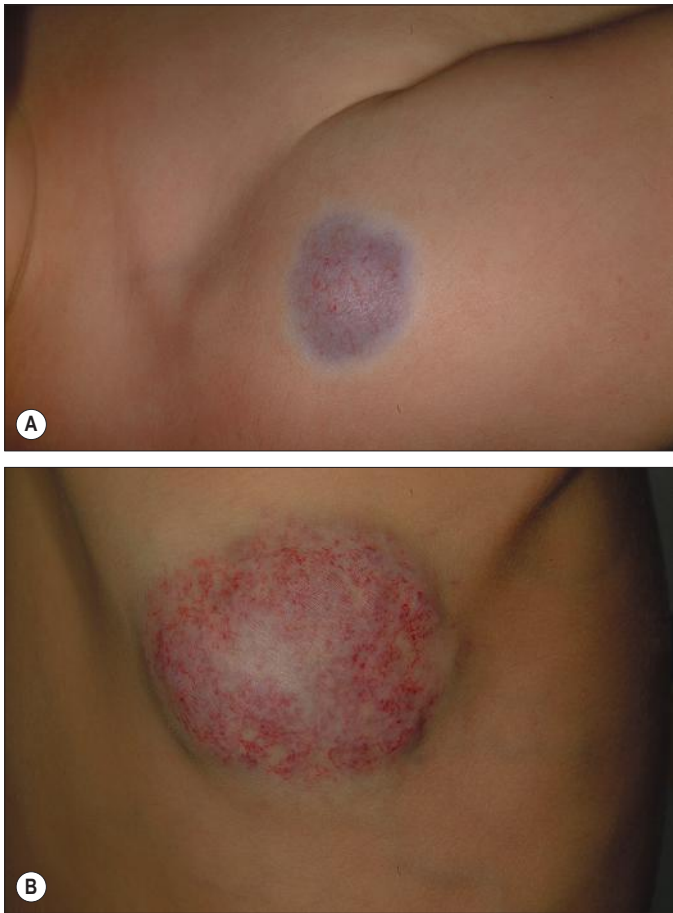


Figure 21.14 Non-involuting congenital hemangioma (NICH). (A) Patch type NICH. A 1-year-old child with unchanged vascular plaque, with coarse telangiectasia and a striking peripheral halo of vasoconstriction. (B) Nodular/tumor type NICH. A 7-year-old child with vascular tumor displaying more dense coarse telangiectasia and significant dermal and subcutaneous tissue involvement.

Etiology and pathogenesis

Congenital hemangiomas are reported equally in males and females with few case series reporting a male predominance. There are no known pre- or perinatal risk factors associated with having a congenital hemangioma and the pathogenesis is unknown.¹⁵⁴ Traditionally, infantile hemangiomas and congenital hemangiomas were considered variants of the same tumor, but an increased understanding of clinical and immunohistochemical differences has clarified the classification and delineated them from one another.^{147,155} Both RICH and NICH demonstrate the proliferative elements seen in vascular tumors like infantile hemangiomas and dysplastic vessels more typically seen in vascular malformations. Moreover, they are Glut-1 negative, further distinguishing them from infantile hemangiomas.^{143,155}

Differential diagnosis

Congenital hemangiomas are usually diagnosed based on clinical characteristics, but Doppler ultrasound and MRI can be helpful. MRI may be considered in the newborn whose tumor has a significant central crust or wound at birth, in order to evaluate the risk for hemorrhage: strikingly, some RICH are

highly vascularized, with large tortuous flow voids on MRI, and others are relatively poorly vascularized, with MRI demonstrating a tumor of intermediate signal on T₁-weighted signal-enhanced sequences. The main differential diagnosis of both RICH and NICH is common infantile hemangioma, but in atypical cases other soft tissue tumors, including malignancies, must be considered. Thrombocytopenia can lead to consideration of other vascular tumors associated with Kasabach–Merritt phenomenon (see below), but the drop in platelet count is usually brief, rather than progressive. A biopsy may occasionally be required.¹⁴²

Occasionally, congenital hemangiomas are noted on routine prenatal ultrasound evaluation and may be mistaken for vascular malformations or other forms of neoplasia. Those that are detected usually reveal prominent vascularity and high flow.

Management

Indications for treatment of RICH include ulceration and bleeding, functional impairment (depending upon location), congestive heart failure, and prominent residual skin changes. Early excision may be particularly important in infants with ulceration or when a necrotic area is present, as there are often large, fast-flow vessels close to the surface, conferring a risk of severe hemorrhage.¹⁵⁶ Indications for treatment of NICH (typically surgical excision) depend on whether their appearance is bothersome, or whether bleeding or pain are present.

TUFTED ANGIOMA AND KAPOSIFORM HEMANGIOENDOTHELIOMA

Tufted angioma (TA) and kaposiform hemangioendothelioma (KHE) are rare vascular tumors with many similar histologic and clinical features.¹⁵⁷ Both are associated with Kasabach–Merritt phenomenon (described below).

Tufted angioma, previously known in the Japanese literature as angioblastoma of Nakagawa, displays pathologic features of vascular tufts of tightly packed capillaries in a typical cannonball distribution, which are diagnostic for this benign vascular tumor.^{158–160} Most cases are acquired early in childhood and may have a protracted course with rare congenital forms reported.¹⁵⁹ Common presenting clinical features are dusky erythematous to violaceous plaques or nodules with thickening over time. Rare multifocal TA are reported.¹⁶¹ Increased hair overlying this tumor is a relatively common finding with increased sweating or pain less commonly seen (Fig. 21.15A–D). TAs may regress completely within a few years, shrink leaving a residuum, or persist unchanged.^{162,163}

Kaposiform hemangioendothelioma is a rare vascular tumor named for its histological resemblance to Kaposi's sarcoma. KHE usually presents in infancy but may appear years later.¹⁶⁴ It often presents as a violaceous to purpuric infiltrative, firm plaque or nodule with rare spontaneous involution. KHE may involve deep tissues and bones, and rare lymph node involvement has been reported without distant metastases.¹⁶⁵ Most reported cases have had associated Kasabach–Merritt phenomenon, but KHE can occur in the absence of a coagulopathy.¹⁶⁶ Both KHE and TA are more common on the extremities and trunk. In the absence of KMP, therapy for TA or KHE is individualized and may include observation, surgical excision, pulsed dye laser and other medical therapies.



Figure 21.15 (C) Tufted angioma with hypertrichosis on the upper arm of an infant. (D) A 6-week-old with lower abdomen blue subcutaneous plaque with overlying central red patch. Biopsy confirmed tufted angioma.

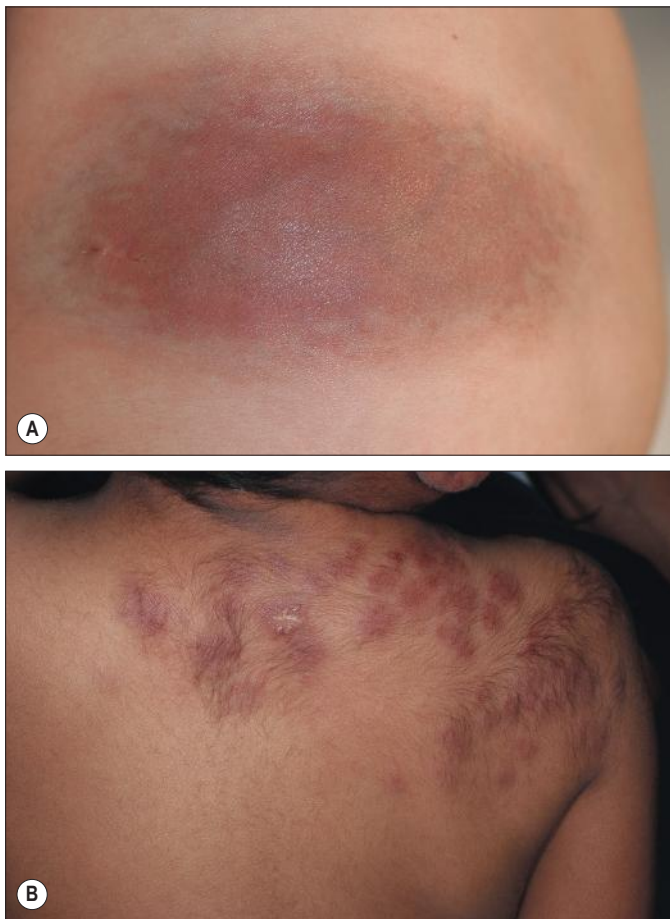


Figure 21.15 (A) A tufted angioma on the flank of a 1-month-old infant. (B) A 2-year-old child with biopsy-confirmed tufted angioma on the posterior shoulder. Hypertrichosis is a common feature.

KASABACH-MERRITT PHENOMENON

Since the first case report in 1940, the label Kasabach–Merritt phenomenon (KMP) has been used to describe infants with vascular anomalies and thrombocytopenia or other coagulopathy, and the syndrome was long considered to be a complication of a ‘hemangioma’.¹⁶⁷ Several publications have now documented that this biologic phenomenon is not associated with a ‘true’ hemangioma of infancy, but rather with other vascular tumors, especially kaposiform hemangioendothelioma (KHE) or tufted angioma (TA), which may occur in association with a lymphatic malformation.^{164,168–171}

Cutaneous findings

Affected infants have a congenital tumor or a lesion noted soon after birth, with subsequent development of an inflammatory, bruising, reddish or purple mass, and purpura. At times, the enlargement of the lesion and affected area can be massive (Fig. 21.16). Before the development of thrombocytopenia and platelet trapping, the clinical appearance may be quite variable as those described above for a TA or KHE. Rarely, an affected newborn may have a history of a congenital bulky tumor detected by prenatal ultrasound.¹⁷²

Extracutaneous findings

Severe thrombocytopenia due to platelet trapping is the hallmark of KMP. Consumption of fibrinogen, elevated D-dimers



Figure 21.16 Kasabach–Merritt phenomenon involving (A) the leg and (B) the neck. Note both the ecchymotic and the inflammatory patterns of the skin.

and anemia are common with KMP. The prothrombin time and the activated partial thromboplastin time are normal to elevated. The coagulopathy occurs to varying degrees, depending on the severity and phase of the disease. KMP has no anatomic site of predilection. Although more cases are within the skin and musculature, KMP can involve deeper visceral structures. Visceral KMP – cervicothoracic, abdominal, pelvic, or intracranial – is life-threatening.

Etiology and pathogenesis

The pathogenesis of TA and KHE is not well understood. They are thought to be derived from lymphatic endothelium, and lymphatic markers. D2-40 is positive in KHE supporting this hypothesis.¹⁷³ These tumors are GLUT-1 negative distinguishing them from infantile hemangiomas.^{65,165} The pathogenesis of KMP is related to platelet trapping within the tumor with later hypofibrinogenemia and fibrinolysis. Surgical procedures or other trauma and infection seem to worsen the coagulopathy in many cases.

Course

Thrombocytopenia may persist for years, but more commonly, it resolves with treatment by 12–18 months of age or sooner. Hemorrhage, sepsis, organ failure or invasion of vital structures may cause death in up to 10–30% of cases. When the hematologic phenomenon is cured, the tumor shrinks but the patient

usually has residual cutaneous changes. The tumor appearance varies from that of a pseudo-port-wine stain, with infiltrated areas and papules, stain-like areas with haloes, and nodular residua, to a poorly-delineated, fibrotic-feeling plaque. In some cases, muscle and joint fibrosis remains with an associated morbidity.¹⁷⁴

Diagnosis

The diagnosis should be suspected in a newborn or young infant with an atypical vascular lesion with the clinical findings described for a TA or KHE. Characteristic thrombocytopenia and hypofibrinogenemia support the diagnosis of TA or KHE. MR imaging may be useful in determining the extent of disease and response to treatment. Skin biopsy may be necessary in atypical cases with the consideration for excess bleeding during the procedure due to the coagulopathy.

Differential diagnosis

Newborns or young infants with malignant soft tissue tumors will occasionally present with a large soft tissue mass and thrombocytopenia. Rarely, mild thrombocytopenia can be present in congenital hemangiomas due to platelet trapping, but this does not become as severe or as persistent as in KMP. In addition, large venous or mixed malformations can have an associated coagulopathy, but elevated D-dimers and consumption of clotting factors, rather than platelet trapping, is noted. Multifocal vascular lesions with an associated thrombocytopenia are more likely to be due to 'multifocal lymphangioendotheliomatosis with thrombocytopenia' than to KMP. Infantile hemangiomas are not associated with a coagulopathy.

Management

Infants with KMP exhibit an inconsistent and variable response to therapeutic regimens and are most often treated with multiple medical agents. Medical therapies include systemic corticosteroids, vincristine, interferon, anti-fibrinolytic agents (tranexamic acid and aminocaproic acid), antiplatelet agents (ticlopidine and aspirin), multi-agent chemotherapy, propranolol and rapamycin.¹⁷⁵⁻¹⁷⁷ Recent expert consensus opinion suggests first-line therapy for KMP with the combination therapy of intravenous vincristine and oral or intravenous corticosteroids.¹⁷⁸ Surgical excision, arterial embolization, and radiation therapy may also benefit some patients. Of note, complete surgical excision is curative but rarely feasible. While platelet transfusions may be required for active bleeding or surgical intervention, they should be otherwise avoided due to the risk of further platelet trapping and tumor enlargement. Care of KMP patients should include an experienced multidisciplinary team that includes a hematologist/oncologist when available.¹⁷⁹

MULTIFOCAL LYMPHANGIOENDOTHELIOMATOSIS WITH THROMBOCYTOPENIA

This rare condition, also called cutaneo-visceral angiomas with thrombocytopenia, is characterized by multifocal congenital and progressive cutaneous and extracutaneous vascular papules and plaques. The vascular skin lesions are variable in number and range in morphology from telangiectatic macules to red-brown plaques to exophytic nodules. Affected infants typically have chronic fluctuating thrombocytopenia and bleeding due to vascular lesions within the GI tract.¹⁸⁰⁻¹⁸² GI bleeding

can be significant with mortality reported. Management is multimodal using both medical and surgical approaches.¹⁸³⁻¹⁸⁵ Other sites of involvement include bones, synovium, lungs, liver, muscle, kidney, spleen, and brain. Skin biopsy specimens demonstrate thin-walled vessels, hobnailed endothelial cells, and intraluminal papillary projections. Vessels stain positive for lymphatic vessel endothelial receptor-1 (LYVE-1).^{180,186}

INFANTILE HEMANGIOPERICYTOMA

Childhood hemangiopericytoma (HPC) is a rare vascularized tumor which is no longer thought of as a vascular tumor, but rather of fibroblastic or myofibroblastic origin.¹⁸⁷ The infantile type, presenting at <1 year of age, is differentiated from the adult type because of its more favorable prognosis with a less aggressive clinical course and good response to chemotherapy.^{134,188} Onset after a year of age holds a similar poorer prognosis to the adult type. The infantile type is more common in boys and usually presents as a firm skin-colored, blue or violaceous dermal or subcutaneous nodule that may become necrotic. Most often cutaneous lesions are located on the head, neck or extremities and are less commonly multicentric with intracranial, mediastinal, abdominal, and lung lesions reported.¹⁸⁹ The better prognosis of the infantile type of HPC and its pathologic features suggests a continuum with infantile myofibromatosis, but this concept and the classification of HPC remains controversial.¹⁹⁰

SPINDLE-CELL HEMANGIOENDOTHELIOMA

Spindle-cell hemangioendothelioma (SCHE) occurs at any age and site but is most commonly reported on the distal extremities. Lesions are solitary or multiple and described as red-brown or blue nodules. Pathology is consistent with a nodular, dense, spindle cell proliferation associated with 'cavernous' vessels of attenuated, irregularly thickened walls. Lesions are treated with excision with local recurrence being common. Metastases have not been reported. Few reported patients with SCHE also had Maffucci syndrome.¹⁹¹

CONGENITAL ECCRINE ANGIOMATOUS HAMARTOMA

Congenital forms of this tumor present as a solitary ill-defined, red-to-blue plaque or nodule, sometimes with lanugo, hyperhidrosis or pain at the site.^{192,193} Lesions are usually located on the extremities or trunk and may spontaneously involute. Rarely are they multifocal. It is not clear whether the reported congenital cases are identical to the slowly growing, persistent acquired form that is characterized by a bluish, brown or erythematous firm nodule or plaque with excess hair, hyperhidrosis, and pain overlying a slow-flow vascular malformation.^{192,194} Diagnosis is established on the basis of characteristic histologic findings which include hyperplasia of normal or dilated eccrine glands in association with dilated capillaries, a variable presence of pilar, lipomatous, mucinous, and lymphatic structure.

PYOGENIC GRANULOMA (LOBULAR CAPILLARY HEMANGIOMA)

Pyogenic granuloma (PG) – also known by its correct histopathologic description 'lobular capillary hemangioma', rather



Figure 21.17 (A) A 2-year-old child with a pyogenic granuloma. This is a very common location for this condition.

than its historic misnomer – is a common vascular tumor of infants and children, albeit relatively rare in the newborn period. PGs usually present as a solitary, red, rapidly growing papule or nodule, often located on the head and neck (Fig. 21.17A,B). They can be pedunculated and often develop an eroded surface and bleed easily and profusely. PGs can occur

within an existing port-wine stain. When a PG occurs in a very young infant, it may be mistaken for an infantile hemangioma, and close examination for the collarette of scale seen in many PGs may help differentiate the two.¹⁹⁵ The differential diagnosis in infants and older children also includes a Spitz nevus. Rare multifocal forms have been observed in newborns, but before specific immunohistochemical identification of infantile hemangiomas was possible they were often mistaken for infantile hemangiomas.^{196–199} PGs do not involute spontaneously, but simple curettage or shave excision followed by electrocautery is usually curative.^{200,201} This quick procedure can often be done under local anesthesia even in young children. Other treatment options include pulsed dye laser for small thin lesions or imiquimod but repeated or prolonged treatment, respectively, may be needed with these modalities.²⁰²

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Figures 13C, D, 15C, D and 17B are available online at [ExpertConsult.com](https://www.expertconsult.com)

Box 3 is available online at [ExpertConsult.com](https://www.expertconsult.com)

KEY REFERENCES

5. Haggstrom AN, Drolet BA, Baselga E, et al. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. *Pediatrics* 2006;118(3): 882–7.
21. Suh KY, Frieden IJ. Infantile hemangiomas with minimal or arrested growth: a retrospective case series. *Arch Dermatol* 2010;146(9): 971–6.
28. Metry D, Heyer G, Hess C, et al. Consensus statement on diagnostic criteria for PHACE syndrome. PHACE Syndrome Research Conference. *Pediatrics* 2009;124(5):1447–56.
29. Haggstrom AN, Garzon MC, Baselga E, et al. Risk for PHACE syndrome in infants with large facial hemangiomas. *Pediatrics* 2010; 126(2):e418–26.
44. Jacobas I, Burrows PE, Frieden IJ, et al. LUMBAR: association between cutaneous infantile hemangiomas of the lower body and regional congenital anomalies. *J Pediatr* 2010;157(5):795–801.e1–e7.
52. Huang SA, Tu HM, Harney JW, et al. Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. *N Engl J Med* 2000;343(3):185–9.
96. Oranje AP, Janmohamed SR, Madern GC, et al. Treatment of small superficial haemangioma with timolol 0.5% ophthalmic solution: a series of 20 cases. *Dermatology* 2011;223(4): 330–4.
114. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008; 358(24):2649–51.
154. Krol A, MacArthur CJ. Congenital hemangiomas: rapidly involuting and noninvoluting congenital hemangiomas. *Arch Facial Plast Surg* 2005;7(5):307–11.
168. Enjolras O, Wassef M, Mazoyer E, et al. Infants with Kasabach–Merritt syndrome do not have ‘true’ hemangioma. *J Pediatr* 1997;130(4): 631–40.



Figure 21.17 (B) Pyogenic granuloma on the cheek of a young child. The glistening red color and lobulated appearance is characteristic.

REFERENCES

- Kilcline C, Frieden IJ. Infantile hemangiomas: how common are they? A systematic review of the medical literature. *Pediatr Dermatol* 2008;25(2):168–73.
- Dickison P, Christou E, Wargon O. A prospective study of infantile hemangiomas with a focus on incidence and risk factors. *Pediatr Dermatol* 2011;28(6):663–9.
- Haggstrom AN, Drolet BA, Baselga E, et al; Hemangioma Investigator Group. Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. *J Pediatr* 2007;150(3):291–4.
- Finn MC, Glowacki J, Mulliken JB. Congenital vascular lesions: clinical application of a new classification. *J Pediatr Surg* 1983;18(6):894–900.
- Haggstrom AN, Drolet BA, Baselga E, et al. Prospective study of infantile hemangiomas: clinical characteristics predicting complications and treatment. *Pediatrics* 2006;118(3):882–7.
- Mulliken JB. Diagnosis and natural history of hemangiomas. In: Mulliken JB, Young AE, editors. *Vascular birthmarks: hemangiomas and malformations*. Philadelphia: WB Saunders; 1988. p. 41–62.
- Drolet BA, Swanson EA, Frieden IJ; Hemangioma Investigator Group. Infantile hemangiomas: an emerging health issue linked to an increased rate of low birth weight infants. *J Pediatr* 2008;153(5):712–15.
- Frieden IJ, Haggstrom AN, Drolet BA, et al. Infantile hemangiomas: current knowledge, future directions. Proceedings of a research workshop on infantile hemangiomas. April 7–9 2005, Bethesda MA. *Pediatr Dermatol* 2005;22(5):383–406.
- López Gutiérrez JC, Avila LF, Sosa G, et al. Placental anomalies in children with infantile hemangioma. *Pediatr Dermatol* 2007;24(4):353–5.
- Burton BK, Schulz CJ, Angle B, et al. An increased incidence of haemangiomas in infants born following chorionic villus sampling (CVS). *Prenat Diagn* 1995;15(3):209–14.
- Blei F, Walter J, Orlow SJ, et al. Familial segregation of hemangiomas and vascular malformations as an autosomal dominant trait. *Arch Dermatol* 1998;134(6):718–22.
- Esterly NB. Cutaneous hemangiomas, vascular stains and malformations, and associated syndromes. *Curr Probl Pediatr* 1996;26(1):3–39.
- Waner M, North PE, Scherer KA, et al. The nonrandom distribution of facial hemangiomas. *Arch Dermatol* 2003;139(7):869–75.
- Chiller KG, Passaro D, Frieden IJ. Hemangiomas of infancy: clinical characteristics, morphologic subtypes and their relationship to race, ethnicity and sex. *Arch Dermatol* 2002;138(12):1567–76.
- Haggstrom AN, Lammer EJ, Schneider RA, et al. Patterns of infantile hemangiomas: new clues to hemangioma pathogenesis and embryonic facial development. *Pediatrics* 2006;117(3):698–703.
- Tollefson MM, Frieden IJ. Early growth of infantile hemangiomas: what parents' photographs tell us. *Pediatrics* 2012;130(2):e314–20.
- Chang LC, Haggstrom AN, Drolet BA, et al; Hemangioma Investigator Group. Growth characteristics of infantile hemangiomas: implications for management. *Pediatrics* 2008;122(2):360–7.
- Brandling-Bennett HA, Metry DW, Baselga E, et al. Infantile hemangiomas with unusually prolonged growth phase: a case series. *Arch Dermatol* 2008;144(12):1632–7.
- Lister WA. The natural history of strawberry nevi. *Lancet* 1938;1:1429–34.
- Corella F, Garcia-Navarro X, Ribe A, et al. Abortive or minimal-growth hemangiomas: Immunohistochemical evidence that they represent true infantile hemangiomas. *J Am Acad Dermatol* 2008;58(4):685–90.
- Suh KY, Frieden IJ. Infantile hemangiomas with minimal or arrested growth: a retrospective case series. *Arch Dermatol* 2010;146(9):971–6.
- Mulliken JB, Marler JJ, Burrows PE, et al. Reticular infantile hemangioma of the limb can be associated with ventral-caudal anomalies, refractory ulceration, and cardiac overload. *Pediatr Dermatol* 2007;24(4):356–62.
- Chamlin SL, Haggstrom AN, Drolet BA, et al. Multicenter prospective study of ulcerated hemangiomas. *J Pediatr* 2007;151(6):684–9, 689.e1.
- Robb R. Refractive errors associated with hemangiomas of the eyelids and orbit in infancy. *Am J Ophthalmol* 1977;83(1):52–8.
- Ceislser EJ, Santos L, Blei F. Periocular hemangiomas: what every physician should know. *Pediatr Dermatol* 2004;21:1–9.
- Haik BG, Jakobiec F, Ellsworth RM, et al. Capillary hemangiomas of the lid and orbit: an analysis of the clinical features and therapeutic results in 101 cases. *Ophthalmology* 1979;86(5):760–89.
- Metry DW, Haggstrom AN, Drolet BA, et al. A prospective study of PHACE syndrome in infantile hemangiomas: demographic features, clinical findings, and complications. *Am J Med Genet A* 2006;140(9):975–86.
- Metry D, Heyer G, Hess C, et al. Consensus statement on diagnostic criteria for PHACE syndrome. PHACE Syndrome Research Conference. *Pediatrics* 2009;124(5):1447–56.
- Haggstrom AN, Garzon MC, Baselga E, et al. Risk for PHACE syndrome in infants with large facial hemangiomas. *Pediatrics* 2010;126(2):e418–26.
- Hess CP, Fullerton HJ, Metry DW, et al. Cervical and intracranial arterial anomalies in 70 patients with PHACE syndrome. *Am J Neuroradiol* 2010;31(10):1980–6.
- Pascual-Castroviejo I, Viano J, Moreno F, et al. Hemangiomas of the head, neck, and chest with associated vascular and brain anomalies: a complex neurocutaneous syndrome. *AJNR Am J Neuroradiol* 1996;17(3):461–71.
- Reese V, Frieden IJ, Paller AS, et al. Association of facial hemangiomas with Dandy-Walker and other posterior fossa malformations. *J Pediatr* 1993;122(3):379–84.
- Geller JD, Topper SE, Hashimoto K. Diffuse neonatal hemangiomatosis: a new constellation of findings. *J Am Acad Dermatol* 1991;245(Pt 2):816–18.
- Burrows PE, Robertson RL, Mulliken JB, et al. Cerebral vasculopathy and neurologic sequelae in infants with cervicofacial hemangioma: report of eight patients. *Radiology* 1998;207(3):601–7.
- Siegel DH, Tefft KA, Kelly T, et al. Stroke in children with posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities (PHACE) syndrome: a systematic review of the literature. *Stroke* 2012;43(6):1672–4.
- Tangtiphaiboonjana J, Hess CP, Bayer M, et al. Neurodevelopmental abnormalities in children with PHACE syndrome. *J Child Neurol* 2013;28(5):608–14.
- Rao RP, Drolet BA, Holland KE, et al. PHACES association: a vasculocutaneous syndrome. *Pediatr Cardiol* 2008;29(4):793–9.
- Wendelin G, Kitzmuller E, Salzer-Muhar U. PHACES: a neurocutaneous syndrome with anomalies of the aorta and supraaortic vessels. *Cardiol Young* 2004;14(2):206–9.
- Duffy KJ, Runge-Samuelson C, Bayer ML, et al. Association of hearing loss with PHACE syndrome. *Arch Dermatol* 2010;146:1391–6.
- Blei F, Orlow SJ, Geronemus RG. Supraumbilical mid-abdominal raphe, sternal atresia, and hemangioma in an infant. *Pediatr Dermatol* 1993;10(1):71–6.
- Frieden IJ, Reese V, Cohen D. PHACE syndrome. The association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. *Arch Dermatol* 1996;132(3):307–11.
- Merheb M, Hourani R, Zantout MS, et al. Endocrine dysfunction in a patient with PHACE syndrome, including port-wine stain of the right periorbital area. *Endocr Pract* 2010;16(2):255–9.
- Poindexter G, Metry DW, Barkovich AJ, et al. PHACE syndrome with intracerebral hemangiomas, heterotopia, and endocrine dysfunction. *Pediatr Neurol* 2007;36(6):402–6.
- Iacobas I, Burrows PE, Frieden IJ, et al. LUMBAR: association between cutaneous infantile hemangiomas of the lower body and regional congenital anomalies. *J Pediatr* 2010;157(5):795–801.e1–7.
- Stockman A, Boralevi F, Taïeb A, et al. SACRAL syndrome: spinal dysraphism, anogenital, cutaneous, renal and urologic anomalies, associated with an angioma of lumbosacral localization. *Dermatology* 2007;214(1):40–5.
- Girard C, Bigorre M, Guillot B, et al. PELVIS Syndrome. *Arch Dermatol* 2006;142(7):884–8.
- Drolet BA, Chamlin SL, Garzon MC, et al. Prospective study of spinal anomalies in children with infantile hemangiomas of the lumbosacral skin. *J Pediatr* 2010;157(5):789–94.
- Schumacher WE, Drolet BA, Maheshwari M, et al. Spinal dysraphism associated with the cutaneous lumbosacral infantile hemangioma: a neuroradiological review. *Pediatr Radiol* 2012;42(3):315–20.
- Garzon MC, Drolet BA, Baselga E, et al; Hemangioma Investigator Group. Comparison of infantile hemangiomas in preterm and term infants: a prospective study. *Arch Dermatol* 2008;144(9):1231–2.
- Horii KA, Drolet BA, Frieden IJ, et al; Hemangioma Investigator Group. Prospective study of the frequency of hepatic hemangiomas in infants with multiple cutaneous infantile hemangiomas. *Pediatr Dermatol* 2011;28(3):245–53.

51. Christison-Lagay ER, Burrows PE, Alomari A, et al. Hepatic hemangiomas: subtype classification and development of a clinical practice algorithm and registry. *J Pediatr Surg* 2007; 42(1):62–8.
52. Huang SA, Tu HM, Harney JW, et al. Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. *N Engl J Med* 2000;343(3):185–9.
53. Konrad D, Ellis G, Perlman K. Spontaneous regression of severe acquired hypothyroidism associated with multiple liver hemangiomas. *Pediatrics* 2003;112(6 Pt 1):1424–6.
54. Ho J, Kendrick V, Dewey D, et al. New insights into the pathophysiology of severe hypothyroidism in an infant with multiple hepatic hemangiomas. *J Pediatr Endocrinol Metab* 2005;18(5):511–14.
55. Orlow SJ, Isakoff MS, Blei F. Increased risk of symptomatic hemangiomas of the airway in association with cutaneous hemangiomas in a 'beard' distribution. *J Pediatr* 1997;131(4):643–6.
56. Suh KY, Rosbe KW, Meyer AK, et al. Extensive airway hemangiomas in two patients without beard hemangiomas. *Pediatr Dermatol* 2011; 28(3):347–8.
57. Haggstrom AN, Skillman S, Garzon MC, et al. Clinical spectrum and risk of PHACE syndrome in cutaneous and airway hemangiomas. *Arch Otolaryngol Head Neck Surg* 2011; 137(7):680–7.
58. Bauland CG, van Steensel MA, Steijlen PM, et al. The pathogenesis of hemangiomas: a review. *Plast Reconstr Surg* 2006;117(2):e29–35.
59. Bischoff J. Monoclonal expansion of endothelial cells in hemangioma: an intrinsic defect with extrinsic consequences? *Trends Cardiovasc Med* 2002;12(5):220–4.
60. Berard M, Sordello S, Ortega N, et al. Vascular endothelial growth factor confers a growth advantage in vitro and in vivo to stromal cells cultured from neonatal hemangiomas. *Am J Pathol* 1997;150(4):1315–26.
61. Boye E, Ying Y, Paranya G, et al. Clonality and altered behavior of endothelial cells from hemangiomas. *J Clin Invest* 2001;107(6):745–52.
62. Walter JW, North PE, Waner M, et al. Somatic mutation of vascular endothelial growth factor receptors in juvenile hemangioma. *Genes Chromosomes Cancer* 2002;33(3):295–303.
63. Yu Y, Varughese J, Brown LF, et al. Increased Tie2 expression, enhanced response to angiopoietin-1, and dysregulated angiopoietin-2 expression in hemangioma-derived endothelial cells. *Am J Pathol* 2001;159(6):2271–80.
64. Berg JN, Walter JW, Thisanagayam U, et al. Evidence for loss of heterozygosity of 5q in sporadic hemangiomas: are somatic mutations involved in hemangioma formation. *J Clin Pathol* 2001;54(3):249–52.
65. North PE, Waner M, Mizeracki A, et al. GLUT1: a newly discovered immunohistochemical marker for juvenile hemangiomas. *Hum Pathol* 2000;31(1):11–22.
66. North PE, Waner M, Mizeracki A, et al. A unique microvascular phenotype shared by juvenile hemangiomas and human placenta. *Arch Dermatol* 2001;137(5):559–70.
67. Barnes CM, Huang S, Kaipainen A, et al. Evidence by molecular profiling for a placental origin of infantile hemangiomas. *Proc Natl Acad Sci USA* 2005;102(52):19097–102.
68. Bree AF, Siegfried E, Sotelo-Avila C, et al. Infantile hemangiomas: speculation on placental trophoblastic origin. *Arch Dermatol* 2001; 137(5):573–7.
69. Takahashi K, Mulliken JB, Kozakewich H, et al. Cellular markers that distinguish the phases of hemangioma during infancy and childhood. *J Clin Invest* 1994;93(6):2357–64.
70. Chang J, Most D, Bresnick S, et al. Proliferative hemangiomas: analysis of cytokine gene expression and angiogenesis. *Plast Reconstr Surg* 1999;103(1):1–9.
71. Zhang L, Lin X, Wang W, et al. Circulating level of vascular endothelial growth factor in differentiating hemangioma from vascular malformation patients. *Plast Reconstr Surg* 2005;116(1):200–4.
72. Jinnin M, Medici D, Park L, et al. Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangiomas. *Nat Med* 2008;14(11):1236–46.
73. Isik FF, Rand RP, Gruss JS, et al. Monocyte chemoattractant protein-1 mRNA expression in hemangiomas and vascular malformations. *J Surg Res* 1996;61(1):71–6.
74. Salcedo R, Ponce ML, Young HA, et al. Human endothelial cells express CCR2 and respond to MCP-1: direct role of MCP-1 in angiogenesis and tumor progression. *Blood* 2000;96(1):34–40.
75. Kraling BM, Razon MJ, Zurakowski D, et al. E-selectin is present in proliferating endothelial cells in human hemangiomas. *Am J Pathol* 1996;148(4):1181–91.
76. Verkarre V, Patey-Mariaud de Serre N, Vazeux R, et al. ICAM-3 and E-selectin endothelial cell expression differentiate two phases of angiogenesis in infantile hemangiomas. *J Cutan Pathol* 1999;26(1):17–24.
77. Tan ST, Velickovic M, Ruger BM, et al. Cellular and extracellular markers of hemangioma. *Plast Reconstr Surg* 2000;106(3):529–38.
78. Marler JJ, Fishman SJ, Kilroy SM, et al. Increased levels of urinary matrix metalloproteinases parallels the extent and activity of vascular anomalies. *Pediatrics* 2005;116(1):38–45.
79. Dadras SS, North PE, Bertoncini J, et al. Infantile hemangiomas are arrested in an early developmental vascular differentiation state. *Mod Pathol* 2004;17(9):1068–79.
80. Bielenberg DR, Bucana CD, Sanchez R, et al. Progressive growth of infantile cutaneous hemangiomas is directly correlated with hyperplasia and angiogenesis of adjacent epidermis and inversely correlated with expression of the endogenous angiogenesis inhibitor, IFN-beta. *Int J Oncol* 1999;14(3):401–8.
81. Ritter MR, Moreno SK, Dorrell MI, et al. Identifying potential regulators of infantile hemangioma progression through large-scale expression analysis: a possible role of the immune system and indoleamine 2,3 dioxygenase (IDO) during involution. *Lymph Res Biol* 2003;1(4):291–9.
82. Ritter MR, Dorrell MI, Edmonds J, et al. Insulin-like growth factor 2 and potential regulators of hemangioma growth and involution identified by large-scale expression analysis. *Proc Natl Acad Sci USA* 2002;99(11):7455–60.
83. Mancini AJ, Smoller BR. Proliferation and apoptosis within juvenile capillary hemangiomas. *Am J Dermatopathol* 1996;18(5):505–14.
84. Razon MJ, Kraling BM, Mulliken JB, et al. Increased apoptosis coincides with onset of involution in infantile hemangiomas. *Microcirculation* 1998;2:189–95.
85. Hasan Q, Ruger BM, Tan ST, et al. Clusterin/apoJ expression during the development of hemangiomas. *Hum Pathol* 2000;31(6):691–7.
86. Pramanik K, Chun CZ, Garnaas MK, et al. Dusp-5 and Snrk-1 coordinately function during vascular development and disease. *Blood* 2009;113(5):1184–91.
87. Dubois J, Alison M. Vascular anomalies: what a radiologist needs to know. *Pediatr Radiol* 2010;40(6):895–905.
88. Konec O, Burrows PE. Magnetic resonance of vascular anomalies. *Magn Reson Imaging Clin N Am* 2002;10(2):363–88, vii.
89. Mulliken JB, Fishman SJ, Burrows PE. Vascular anomalies. *Curr Probl Surg* 2000;37(8):517–84.
90. Frieden IJ, Rogers M, Garzon MC. Conditions masquerading as infantile haemangioma: Part 1. *Australas J Dermatol* 2009;50(2):77–97.
91. Frieden IJ, Rogers M, Garzon MC. Conditions masquerading as infantile haemangioma: Part 2. *Australas J Dermatol* 2009;50(3):153–68.
92. Tanner JL, Dechert MP, Frieden IJ. Growing up with a facial hemangioma: parent and child coping and adaptation. *Pediatrics* 1998;101(3 Pt 1):446–52.
93. Cruz OA, Zarnegar SR, Myers SE. Treatment of periorbital capillary hemangioma with topical clobetasol propionate. *Ophthalmology* 1995; 102(12):2012–15.
94. Garzon MC, Lucky AW, Hawrot A, et al. Ultra-potent topical corticosteroid treatment of hemangiomas of infancy. *J Am Acad Dermatol* 2005;52(2):281–6.
95. Pandey A, Gangopadhyay AN, Sharma SP, et al. Evaluation of topical steroids in the treatment of superficial hemangioma. *Skinmed* 2010; 8(1):9–11.
96. Oranje AP, Janmohamed SR, Madern GC, et al. Treatment of small superficial haemangioma with timolol 0.5% ophthalmic solution: a series of 20 cases. *Dermatology* 2011;223(4):330–4.
97. Odeh M, Oliven A, Bassan H. Timolol eyedrop-induced fatal bronchospasm in an asthmatic patient. *J Fam Pract* 1991;32(1):97–8.
98. Shedden AH, Laurence J, Barrish A, et al. Plasma timolol concentrations of timolol maleate: timolol gel-forming solution (TIMOPTIC-XE) once daily versus timolol maleate ophthalmic solution twice daily. *Doc Ophthalmol* 2001;103(1):73–9.
99. Moehrle M, Léauté-Labrèze C, Schmidt V, et al. Topical Timolol for small hemangiomas of infancy. *Pediatr Dermatol* 2012;30(2):245–9.
100. Chakkittakandiyil A, Phillips R, Frieden IJ, et al. Timolol maleate 0.5% or 0.1% gel-forming solution for infantile hemangiomas: a retrospective, multicenter, cohort study. *Pediatr Dermatol* 2012;29(1):28–31.
101. Martinez MI, Sanchez-Carpintero I, North PE, et al. Infantile hemangioma: clinical resolution with 5% imiquimod cream. *Arch Dermatol* 2002;138(7):881–4.
102. Jiang C, Hu X, Ma G, et al. A prospective self-controlled phase II study of imiquimod 5% cream in the treatment of infantile hemangioma. *Pediatr Dermatol* 2011;28(3):259–66.
103. McCuaig CC, Dubois J, Powell J, et al. A phase II, open-label study of the efficacy and safety of imiquimod in the treatment of superficial and mixed infantile hemangioma. *Pediatr Dermatol* 2009;26(2):203–12.

104. Shorr N, Seiff SR. Central retinal artery occlusion associated with periocular corticosteroid injection for juvenile hemangioma. *Ophthalmol Surg* 1986;17(4):229–31.
105. Egbert JE, Schwartz GS, Walsh AW. Diagnosis and treatment of an ophthalmic artery occlusion during an intralesional injection of corticosteroid into an eyelid capillary hemangioma. *Am J Ophthalmol* 1996;121(6):638–42.
106. Goyal R, Watts P, Lane CM, et al. Adrenal suppression and failure to thrive after steroid injections for periocular hemangioma. *Ophthalmology* 2004;111(2):389–95.
107. Garden JM, Bakus AD, Paller AS. Treatment of cutaneous hemangiomas by the flashlamp-pumped pulsed dye laser: prospective analysis. *J Pediatr* 1992;120(4 Pt 1):555–60.
108. Hohenleutner S, Badur-Ganter E, Landthaler M, et al. Long-term results in the treatment of childhood hemangioma with the flashlamp-pumped pulsed dye laser: an evaluation of 617 cases. *Lasers Surg Med* 2001;28(3):273–7.
109. Ashinoff R, Geronemus RG. Failure of the flashlamp-pumped pulsed dye laser to prevent progression to deep hemangioma. *Pediatr Dermatol* 1993;10(1):77–80.
110. Batta K, Goodyear HM, Moss C, et al. Randomised controlled study of early pulsed-dye laser treatment of uncomplicated childhood haemangiomas: results of a 1-year analysis. *Lancet* 2002;360(9332):521–7.
111. Witman PM, Wagner AM, Scherer K, et al. Complications following pulsed dye laser treatment of superficial hemangiomas. *Lasers Surg Med* 2006;38(2):116–23.
112. Morelli JG, Tan OT, Weston WL. Treatment of ulcerated hemangiomas with the pulsed tunable dye laser. *Am J Dis Child* 1991;145(9):1062–4.
113. David LR, Malek MM, Argenta LC. Efficacy of pulse dye laser therapy for the treatment of ulcerated hemangiomas: a review of 78 patients. *Br J Plast Surg* 2003;56(4):317–27.
114. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008;358(24):2649–51.
115. Bertrand J, Sammour R, McCuaig C, et al. Propranolol in the treatment of problematic infantile hemangioma: review of 35 consecutive patients from a vascular anomalies clinic. *J Cutan Med Surg* 2012;16(5):317–23.
116. Schupp CJ, Kleber JB, Günther P, et al. Propranolol therapy in 55 infants with infantile hemangioma: dosage, duration, adverse effects, and outcome. *Pediatr Dermatol* 2011;28(6):640–4.
117. Zvulunov A, McCuaig C, Frieden IJ, et al. Oral propranolol therapy for infantile hemangiomas beyond the proliferation phase: a multicenter retrospective study. *Pediatr Dermatol* 2011;28(2):94–8.
118. Raol N, Metry D, Edmonds J, et al. Propranolol for the treatment of subglottic hemangiomas. *Int J Pediatr Otorhinolaryngol* 2011;7512:1510–14.
119. Chim H, Armijo BS, Miller E, et al. Propranolol induces regression of hemangioma cells through HIF-1 α -mediated inhibition of VEGF-A. *Ann Surg* 2012;256(1):146–56.
120. Chisholm KM, Chang KW, Truong MT, et al. β -Adrenergic receptor expression in vascular tumors. *Mod Pathol* 2012;25(1):144–51.
121. Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. *Pediatrics* 2013;131(1):128–40.
122. Holland KE, Frieden IJ, Frommelt PC, et al. Hypoglycemia in children taking propranolol for the treatment of infantile hemangioma. *Arch Dermatol* 2010;146(7):775–8.
123. Breur JM, de Graaf M, Breugem CC, et al. Hypoglycemia as a result of propranolol during treatment of infantile hemangioma: a case report. *Pediatr Dermatol* 2011;28(2):169–71.
124. Bagazgoitia L, Hernández-Martín A, Torrelo A. Recurrence of infantile hemangiomas treated with propranolol. *Pediatr Dermatol* 2011;28(6):658–62.
125. Metry D, Frieden IJ, Hess C, et al. Propranolol use in PHACE syndrome with cervical and intracranial arterial anomalies: collective experience in 32 infants. *Pediatr Dermatol* 2013;30(1):71–89.
126. Izadpanah A, Izadpanah A, Kanevsky J, et al. Propranolol versus corticosteroids in the treatment of infantile hemangioma: a systematic review and meta-analysis. *Plast Reconstr Surg* 2013;131(3):601–13.
127. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. *N Engl J Med* 1999;341(3):173–81.
128. Bennett ML, Fleischer AB Jr, Chamlin SL, et al. Oral corticosteroid use is effective for cutaneous hemangiomas: an evidence-based evaluation. *Arch Dermatol* 2001;137(9):1208–13.
129. Boon LM, MacDonald DM, Mulliken JB. Complications of systemic corticosteroid therapy for problematic hemangioma. *Plast Reconstr Surg* 1999;104(6):1616–23.
130. George ME, Sharma V, Jacobson J, et al. Adverse effects of systemic glucocorticosteroid therapy in infants with hemangiomas. *Arch Dermatol* 2004;140(8):963–9.
131. Aviles R, Boyce TG, Thompson DM. Pneumocystis carinii pneumonia in a 3-month-old infant receiving high-dose corticosteroid therapy for airway hemangiomas. *Mayo Clin Proc* 2004;79(2):243–5.
132. Halliday HL. The effect of postnatal steroids on growth and development. *J Perinat Med* 2001;29(4):281–5.
133. Chang E, Boyd A, Nelson CC, et al. Successful treatment of infantile hemangiomas with interferon- α -2b. *J Pediatr Hematol Oncol* 1997;19(3):237–44.
134. Tamayo L, Ortiz D, Orozco-Covarrubias L, et al. Therapeutic efficacy of interferon α -2b in infants with life-threatening giant hemangiomas. *Arch Dermatol* 1997;133(12):1567–71.
135. Dubois J, Hershon DJ, Carman L, et al. Toxicity profile of interferon α -2b in children: A prospective evaluation. *J Pediatr* 1999;135(6):782–5.
136. Michaud AP, Bauman NM, Burke DK, et al. Spastic diplegia and other motor disturbances in infants receiving interferon α . *Laryngoscope* 2004;114(7):1231–6.
137. Haisley-Royster C, Enjolras O, Frieden IJ, et al. Kasabach-Merritt phenomenon: a retrospective study of treatment with vincristine. *J Pediatr Hematol Oncol* 2002;24(6):459–62. Erratum in: *J Pediatr Hematol Oncol* 2002;24(9):794.
138. Adams DM. The nonsurgical management of vascular lesions. *Facial Plast Clin North Am* 2001;9(4):601–8.
139. Perez Payarols P, Pardo Masferrer J, Gomez Bellvert C. Treatment of life-threatening hemangiomas with vincristine. *N Engl J Med* 1995;333(1):69.
140. Kim HJ, Colombo M, Frieden IJ. Ulcerated hemangiomas: clinical characteristics and response to therapy. *J Am Acad Dermatol* 2001;44(6):962–72.
141. Metz BJ, Rubenstein MC, Levy ML, et al. Response of ulcerated perineal hemangiomas of infancy to becaplermin gel, a recombinant human platelet-derived growth factor. *Arch Dermatol* 2004;140(7):867–70.
142. Boon LM, Enjolras O, Mulliken JB. Congenital hemangioma: evidence of accelerated involution. *J Pediatr* 1996;128(3):329–35.
143. North PE, Waner M, James CA, et al. Congenital nonprogressive hemangioma: a distinct clinicopathologic entity unlike infantile hemangioma. *Arch Dermatol* 2001;137(12):1607–20.
144. Browning JC, Metry DW. Rapidly involuting congenital hemangioma: a case report and review of the literature. *Dermatol Online J* 2008;14(4):11.
145. Mulliken JB, Bischoff J, Kozakewich HP. Multifocal rapidly involuting congenital hemangioma: a link to chorangioma. *Am J Med Genet A* 2007;143A(24):3038–46.
146. Ozcan UA. Rapidly involuting congenital hemangioma: a case of complete prenatal involution. *J Clin Ultrasound* 2010;38:85–8.
147. Mulliken JB, Enjolras O. Congenital hemangiomas and infantile hemangioma: missing links. *J Am Acad Dermatol* 2004;50(6):875–82.
148. Nolan M, Hartin CW Jr, Pierre J, et al. Life-threatening hemorrhage from a congenital hemangioma caused by birth trauma. *J Pediatr Surg* 2012;47(5):1016–18.
149. Powell J, Blouin MM, David M, et al. Bleeding in congenital hemangiomas: crusting as a clinical predictive sign and usefulness of tranexamic acid. *Pediatr Dermatol* 2012;29(2):182–5.
150. Roebuck D, Sebire N, Lehmann E, et al. Rapidly involuting congenital hemangioma (RICH) of the liver. *Pediatr Radiol* 2012;42(3):308–14.
151. Zenzen W, Perez-Atayde AR, Elisofon SA, et al. Hepatic failure in a rapidly involuting congenital hemangioma of the liver: failure of embolotherapy. *Pediatr Radiol* 2009;3910:1118–23.
152. Baselga E, Cordisco MR, Garzon M, et al. Rapidly involuting congenital hemangioma associated with transient thrombocytopenia and coagulopathy: a case series. *Br J Dermatol* 2008;158(6):1363–70.
153. Hsiao CH, Tsao PN, Hsieh WS, et al. Huge, alarming congenital hemangioma of the scalp presenting as heart failure and Kasabach-Merritt syndrome: a case report. *Eur J Pediatr* 2007;166(6):619–20.
154. Krol A, MacArthur CJ. Congenital hemangiomas: rapidly involuting and noninvoluting congenital hemangiomas. *Arch Facial Plast Surg* 2005;7(5):307–11.
155. Berenguer B, Mulliken JB, Enjolras O, et al. Rapidly involuting congenital hemangioma: clinical and histopathologic features. *Pediatr Dev Pathol* 2003;6(6):495–510.
156. Enjolras O, Picard A, Soupre V. [Congenital haemangiomas and other rare vascular tumors]. *Ann Chir Plast Esthet* 2006;51(4–5):339–46.
157. Chu CY, Hsiao CH, Chiu HC. Transformation between kaposiform hemangioendothelioma and tufted angioma. *Dermatology* 2003;206:334–7.

158. Wilson-Jones E, Orkin M. Tufted angioma (angioblastoma): a benign progressive angioma not to be confused with Kaposi's sarcoma or low grade angiosarcoma. *J Am Acad Dermatol* 1989;20(2 Pt 1):214–25.
159. Catteau B, Enjolras O, Delaporte E, et al. Sclerosing tufted angioma. Apropos of 4 cases involving lower limbs. *Ann Dermatol Venerol* 1998;12510:682–7.
160. Cho KH, Kim SH, Park KC, et al. Angioblastoma (Nakagawa)—is it the same as tufted angioma? *Clin Exp Dermatol* 1999;16(2):110–13.
161. Maronn M, Chamlin S, Metry D. Multifocal tufted angiomas in 2 infants. *Arch Dermatol* 2009;145(7):847–8.
162. Lam WY, Mac-Moune Lai F, Look CN, et al. Tufted angioma with complete regression. *J Cutan Pathol* 1994;21(5):461–6.
163. Ishikawa K, Hatano Y, Ichikawa H, et al. The spontaneous regression of tufted angioma. A case of regression after two recurrences and a review of 27 cases reported in the literature. *Dermatology* 2005;210(4):346–8.
164. Vin-Christian K, McCalmont TH, Frieden IJ. Kaposiform hemangioendothelioma. An aggressive, locally invasive vascular tumor that can mimic hemangioma of infancy. *Arch Dermatol* 1997;133(12):1573–8.
165. Lyons LL, North PE, Mac-Moune Lai F, et al. Kaposiform hemangioendothelioma. A study of 33 cases emphasizing its pathologic, immunophenotypic, and biologic uniqueness from juvenile hemangioma. *Am J Surg Pathol* 2004;28(5):559–68.
166. Gruman A, Liang MG, Mulliken JB, et al. Kaposiform hemangioendothelioma without Kasabach-Merritt phenomenon. *J Am Acad Dermatol* 2005;52(4):616–22.
167. Kasabach HH, Merritt KK. Capillary hemangioma with extensive purpura, report of a case. *Am J Dis Child* 1940;59:1063–70.
168. Enjolras O, Wassef M, Mazoyer E, et al. Infants with Kasabach-Merritt syndrome do not have 'true' hemangioma. *J Pediatr* 1997;130(4):631–40.
169. Tsang WY, Chan JK. Kaposi-like hemangioendothelioma: a distinctive vascular neoplasm of the retroperineum. *Am J Surg Pathol* 1991;1510:982–9.
170. Niedt GW, Greco MA, Wiczorek R, et al. Hemangioma with Kaposi's sarcoma-like features: report of two cases. *Pediatr Pathol* 1989;9(5):567–75.
171. Sarkar M, Mulliken JB, Kozakewich HPW, et al. Thrombocytopenic coagulopathy (Kasabach-Merritt phenomenon) is associated with kaposiform hemangioendothelioma and not with common infantile hemangioma. *Plast Reconstr Surg* 1997;100(6):1377–86.
172. Raman S, Ramanujam T, Lim CT. Prenatal diagnosis of an extensive haemangioma of the fetal leg: a case report. *J Obstet Gynecol Res* 1996;22(4):375–8.
173. Debelenko LV, Perez-Atayde AR, Mulliken JB, et al. D2–40 immunohistochemical analysis of pediatric vascular tumors reveal positivity in kaposiform hemangioendothelioma. *Mod Pathol* 2005;1811:1454–60.
174. Enjolras O, Mulliken JB, Wassef M, et al. Residual lesions after Kasabach-Merritt phenomenon in 41 patients. *J Am Acad Dermatol* 2000;42(2 Pt 1):225–35.
175. Blei F, Karp N, Rofsky N, et al. Successful multimodal therapy for kaposiform hemangioendothelioma complicated by Kasabach-Merritt phenomenon: case report and review of the literature. *Pediatr Hematol Oncol* 1998;15(4):295–305.
176. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer* 2011;57(6):1018–24.
177. Chui YE, Drolet BA, Blei F, et al. Variable response to propranolol treatment of kaposiform hemangioendothelioma, tufted angioma, and Kasabach-Merritt phenomenon. *Pediatr Blood Cancer* 2012;59(5):934–8.
178. Drolet BA, Trenor CC, Brandao LR, et al. Consensus-derived practice standards plan for complicated Kaposiform hemangioendothelioma. *J Pediatr* 2013;163(1):285–91.
179. Enjolras O, Wassef M, Dosquet C, et al. Kasabach-Merritt syndrome on a congenital tufted angioma. *Ann Dermatol Venerol* 1998;125(4):257–60.
180. North PE, Kahn T, Cordisco MR, et al. Multifocal lymphangioendotheliomatosis with thrombocytopenia: a newly recognized clinicopathologic entity. *Arch Dermatol* 2004;140(5):599–606.
181. Maronn M, Catrine K, North P, et al. Expanding the phenotype of multifocal lymphangioendotheliomatosis with thrombocytopenia. *Pediatr Blood Cancer* 2009;52(4):531–4.
182. Glick ZR, Frieden IJ, Garzon MC, et al. Diffuse neonatal hemangiomatosis: an evidence-based review of case reports in the literature. *J Am Acad Dermatol* 2012;67(5):895–903.
183. Esparza EM, Deutsch G, Stanescu L, et al. Multifocal lymphangioendotheliomatosis with thrombocytopenia: phenotypic variant and course with propranolol, corticosteroids and aminocaproic acid. *J Am Acad Dermatol* 2012;67(1):e62–4.
184. Kline RM, Buck LM. Bevacizumab treatment in multifocal lymphangioendotheliomatosis with thrombocytopenia. *Pediatr Blood Cancer* 2009;52(4):534–6.
185. Noel RJ, Duffy KJ, Kelly ME, et al. Endoscopic management of gastrointestinal bleeding from multifocal lymphangioendotheliomatosis with thrombocytopenia: limited efficacy with complications. *J Pediatr Gastroenterol Nutr* 2012;54(6):822–4.
186. Prasad V, Fishman S, Mulliken JB, et al. Cutaneous visceral angiomatosis with thrombocytopenia. *Pediatr Dev Pathol* 2005;8(4):407–19.
187. Enzinger FM, Weiss SW. Infantile myofibromatosis. In: *Soft tissue tumors*. 3rd ed. St Louis: Mosby; 1995. p. 77–83.
188. Fernandez-Pineda I, Parida L, Jenkins JJ, et al. Childhood hemangiopericytoma: review of St. Jude Children's Research Hospital. *J Pediatr Hematol Oncol* 2011;33(5):356–9.
189. Sulit DJ, Tom WL, Willert JR, et al. Multicentric infantile hemangiopericytoma: case report and review of the literature. *J Pediatr Hematol Oncol* 2011;33(4):e166–70.
190. Fletcher CD. The evolving classification of soft tissue tumours: an update based on the new WHO classification. *Histopathology* 2006;48(1):3–12.
191. Perkins P, Weiss SW. Spindle cell hemangioendothelioma: an analysis of 78 cases with reassessment of its pathogenesis and biologic behavior. *Am J Surg Pathol* 1996;2010:1196–204.
192. Nakatsui TC, Schloss E, Krol A, et al. Eccrine angiomatous hamartoma: report of a case and literature review. *J Am Acad Dermatol* 1999;41(1):109–11.
193. Larralde M, Bazzolo E, Boggio P, et al. Eccrine angiomatous hamartoma: report of five congenital cases. *Pediatr Dermatol* 2009;26(3):316–19.
194. SanMartin O, Botella R, Alegre V, et al. Congenital eccrine angiomatous hamartoma. *Am J Dermatopathol* 1992;14(2):161–4.
195. Frieden IJ, Esterly NB. Pyogenic granulomas of infancy masquerading as strawberry hemangiomas. *Pediatrics* 1992;90(3):989–91.
196. Ho V, Krol A, Bhargava R, et al. Diffuse neonatal haemangiomatosis. *J Paediatr Child Health* 2000;36(3):286–9.
197. Rothe MJ, Rowse D, Grant-Kels JM. Benign neonatal hemangiomatosis with aggressive growth of cutaneous lesions. *Pediatr Dermatol* 1991;8(2):140–6.
198. Browning JC, Eldin KW, Kozakewich HP, et al. Congenital disseminated pyogenic granulomas. *Pediatr Dermatol* 2009;26(3):323–7.
199. Baselga E, Wassef M, Lopez S, et al. Agminated, eruptive pyogenic granuloma-like lesions developing over congenital vascular stains. *Pediatr Dermatol* 2012;29(2):186–90.
200. Patrice SJ, Wiss K, Mulliken JB. Pyogenic granuloma (lobular capillary hemangioma): a clinicopathologic study of 178 cases. *Pediatr Dermatol* 1991;8(4):267–76.
201. Pagliai KA, Cohen BA. Pyogenic granuloma in children. *Pediatr Dermatol* 2004;21(1):10–13.
202. Tritton SM, Smith S, Wong LC, et al. Pyogenic granuloma in ten children treated with topical imiquimod. *Pediatr Dermatol* 2009;26(3):269–72.

Introduction to vascular malformations

In 1982, Mulliken and Glowacki¹ proposed a biologic classification of vascular birthmarks that has become widely accepted. It was modified slightly in 1996 by the International Society for the Study of Vascular Anomalies (ISSVA).² Two major groups of vascular birthmarks are recognized: vascular malformations, which are composed of dysplastic, malformed vessels; and vascular tumors, which demonstrate cellular hyperplasia. The distinction between malformations and tumors is emphasized by their varying histologic appearance, cellular markers, and natural history (see [Chapter 21](#) for a full review of vascular tumors).^{3,4} The ISSVA classification of vascular anomalies allows for more precise diagnoses and helps avoid the perpetuation of out-dated terminology such as ‘cavernous hemangioma,’ which has been previously used to describe both tumors and malformations ([Table 22.1](#)).³

Vascular malformations are subcategorized according to flow characteristics and predominant anomalous channels. They can occur alone or in combination: slow-flow malformations (capillary, C; venous, V; lymphatic, L) or fast-flow malformations (arteriovenous malformation, AVM; and arteriovenous fistula, AVF). Vascular malformations are often localized and circumscribed lesions, but can also present in a segmental/regional pattern or in a multifocal, disseminated form. Vascular malformations can also be observed in the setting of various syndromes, many of which arise due to known genetic mutations. In several cases, the discovery of the genetic mutation has advanced our understanding of the pathogenesis of the underlying conditions. A number of complex and/or combined vascular malformations also exist: CVM, CLVM, LVM, AVM, CAVM, CLAVM, and so forth, with some of them known by eponyms. In this chapter, we discuss a variety of these sometimes eponymous syndromes associated with vascular malformations. We have grouped them according to their predominant malformation but recognize these categories are not always rigid and significant overlap exists.

Capillary malformations

NEVUS SIMPLEX (SALMON PATCH, FADING CAPILLARY STAIN)

A salmon patch is a capillary malformation (CM), also known as an ‘angel kiss’ when located on the forehead or eyelids, and ‘stork bite’ when located on the nape of the neck. It is present in nearly half of all newborns and affects males and females equally. It has a characteristic predilection for the midline, with the most common locations being the nape, upper glabella, nose, and upper lip ([Fig. 22.1](#)). The occiput and lower back may

also be affected.⁵ If a salmon patch involves the upper eyelid and does not occur concomitantly with the classic V-shaped patch in the middle of the forehead, it may be difficult to differentiate from a partial V1 port-wine stain or a hemangioma precursor. Occasionally, widespread involvement of nevus simplex at many different sites can exist – the term ‘nevus simplex complex’ has recently been proposed to describe such cases in an attempt to prevent confusion with port-wine stains.⁶ Nevus simplex usually disappears within 1 or 2 years, but some persist, particularly those at the nape.⁷

A nevus simplex localized to the midline sacral region has sometimes been referred to as a ‘butterfly-shaped mark’. Involvement at this site is most often seen in infants with multiple salmon patches elsewhere. In most cases, these are benign and not associated with underlying spinal dysraphism. However, prospective studies with MR imaging are lacking, so it is not possible to exclude this risk completely. In the absence of any other concerning signs, a nevus simplex in this location is usually innocent.

Although nevus simplex usually do not have underlying associations, rarely they are a manifestation of certain syndromes, such as Beckwith–Wiedemann, macrocephaly–capillary malformation (MCM/MCAP), or Nova syndromes (see below).

CAPILLARY MALFORMATIONS

The terms port-wine stain (PWS) and capillary malformation (CM) are used interchangeably. CMs are almost always evident at birth and found in up to 0.3% of newborns.⁸ They are mostly sporadic in origin. Histopathologically, they are comprised of normal capillaries within the superficial dermis without evidence of proliferation. CMs can be observed in the setting of several different syndromes discussed later in this chapter.

Pathogenesis

The etiology of CM is not fully understood, however recent reports of mutations in *GNAQ* in both syndromic and non-syndromic CMs point to an underlying genetic basis.⁹ Another familial form of CM occurring with AVM has been reported in the CM-AVM syndrome.

Cutaneous findings

PWS are pink or red patches that typically grow proportionately with the child’s somatic growth, and persist throughout the patient’s life. They consist of ectatic dermal capillaries and may occur anywhere on the body ([Fig. 22.2A](#)). PWS may appear to lighten over the first 3–6 months of life, but this should not be taken as a sign of resolution. Rather, this physiologic lightening is due to the decrease in blood hemoglobin concentration corresponding to the change from fetal to adult type hemoglobin ([Fig. 22.2B](#)).¹⁰ Capillary malformations can occur anywhere on

TABLE 22.1 ISSVA Classification of vascular anomalies

Vascular tumors	Vascular malformations
Infantile hemangioma Congenital hemangioma (RICH, NICH) Kaposiform hemangioendothelioma (with or without Kasabach–Merritt phenomenon) Tufted angioma (with or without Kasabach–Merritt phenomenon) Spindle cell hemangioendothelioma Other rare hemangioendotheliomas (epithelioid, Dabska, lymphangioendotheliomatosis, etc.) Dermatologic acquired vascular tumors (pyogenic granuloma, glomeruloid hemangioma, targetoid hemangioma, etc.)	Slow-flow malformations: Capillary malformation Port-wine stain Telangiectasia Angiokeratoma Venous malformation Common sporadic Familial venous malformation cutaneous and mucosal (VMCM) Glomuvenous malformation (GVM) Lymphatic malformation (LM) Fast-flow malformations: Arteriovenous malformation (AVM) Arterial malformation (AM) Arteriovenous fistula (AVF) Complex combined malformations (CVM, CLM, LVM, CLVM, AVM-LM, CM-AVM)

(Mulliken and Glowacki 1982; The International Society for the Study of Vascular Anomalies, ISSVA 1996, 2003)

Adapted from Enjolras O, Wassef M, Chapot R. *Color atlas of vascular tumors and vascular malformations*. New York, NY: Cambridge University Press; 2007.



Figure 22.1 Typical nevus simplex on the mid-forehead and upper eyelid.

the body. They may or may not be associated with overgrowth of the affected area (Fig. 22.2). Port-wine stains on the face tend to follow a dermatomal pattern, respecting the trigeminal nerve V1–V3 distribution

or comprising multiple dermatomes (Fig. 22.3). The natural history of port-wine stains over a lifetime is often one of gradual darkening from pink-red to a crimson or deep purple hue. Skin thickening and soft tissue and/or bony hypertrophy may also develop. Eczematous changes can occur in PWS and salmon patches, either with or without treatment. Nodular vascular lesions (pyogenic granulomas) may appear within PWS during childhood or adult life and may require surgical intervention.¹¹ The association of PWS with pigmentary anomalies such as extensive Mongolian spots, nevus spilus, or nevoid hyperpigmentation is a feature of phakomatosis pigmentovascularis (see further discussion of this entity below, Fig. 22.4, Table 22.2).

Extracutaneous findings

Progressive soft tissue and bony overgrowth may occur during childhood, especially with V2 PWS, and subtle changes are sometimes noted even in the neonatal period.¹² Asymmetric maxillary hypertrophy associated with distortion of the facial

features requires multidisciplinary management with orthodontic follow-up and treatment. Some patients require procedures to correct skeletal overgrowth in late childhood. Gingival hypertrophy may also develop. Port-wine stains are also a manifestation of several different syndromes with other extracutaneous features discussed later in the chapter (see ‘Syndromes associated with vascular malformations’, below).

Management

The gradual thickening and nodularity of PWS provide a medical rationale for treatment during infancy and childhood.¹¹ The flashlamp-pumped pulsed dye laser (PDL) is the gold standard treatment for PWS and poses a very low risk of scarring, even in young infants. It has been used for longer than 15 years and advances such as the development of a cooling system have improved efficacy. Most PDL units have a wavelength of 595 nm. Settings of 0.45–1.5 ms pulse duration, 6–10 J/cm² fluences, and 7–10 mm spot size along with the coolant system (dynamic cooling device) are used in the majority of cases. Although only 15–20% of PWS clear completely with PDL, the majority of treated lesions lighten significantly.^{13,14} Response to laser treatment varies by area and skin type: outcomes are better on the face and neck, albeit with less improvement in V2 than other facial sites, and are also better in patients with type I–II skin.¹⁴ The extremities do not respond as well.^{13–15} Controversy exists regarding the age at which treatment should begin. Some authors have noted a better therapeutic response with fewer treatments when treatment was initiated in early infancy,¹⁶ but others have found no difference.¹⁷ Treating earlier (in infancy or early childhood) can be helpful in reducing stigmatization and may help prevent thickening of the skin.¹⁸ Treating early in infancy may enable the physician to treat with topical anesthesia, as small infants can be swaddled and held during a brief treatment and local anesthetic can be applied prior to the procedure. In older children with large stains, general anesthesia may be required. In most cases, re-darkening occurs with time and touch-up treatments are often needed in later childhood or teen years.¹⁹

In treatment-resistant CM, other laser modalities have recently been studied in an attempt to decrease thickness, color,



Figure 22.2 (A) Neonate with extensive capillary malformation of the back, upper extremities and left leg; also note infantile hemangioma on the right leg. (B) Same patient aged 1, with subtle overgrowth of the affected limb. Note also the physiologic lightening of the stain with time.



Figure 22.3 Port-wine stain involving left facial V1 + V2 + V3 and right V3 areas. The V1 involvement indicates a risk of Sturge-Weber syndrome, which this infant had.



Figure 22.4 Phakomatosis pigmentovascularis. (Courtesy of H.P. Makkar.)

TABLE 22.2 Classification of phakomatosis pigmentovascularis				
Traditional classification	Alternate (Happle) classification	Vascular anomaly	Pigment anomaly	Other
I	–	CM	Epidermal nevus	–
II	Cesioflammea	CM	Dermal melanosis (Mongolian spots, Nevus of Ota)	± Nevus anemicus
III	Spilorosea	CM	Nevus spilus	± Nevus anemicus
IV	Unclassifiable	CM	Dermal melanosis (Mongolian spots, Nevus of Ota)	± Nevus anemicus
V	Cesiomarmorata	CMTC	Nevus spilus Dermal melanosis	–

and nodularity. These include the long-pulsed neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, the combined PDL and Nd:YAG laser, and the alexandrite laser.^{20–24}

Other novel therapies show some initial promise, including intense pulsed light (IPL), photodynamic therapy (PDT), and application of topical anti-angiogenic factors (imiquimod and rapamycin) in conjunction with laser ablation.^{25–35}

In cases where there is soft tissue or bony overgrowth, or in syndromic CM, a multidisciplinary approach to management is often necessary. Patients may require orthodontic work, maxillofacial reconstruction or soft tissue debulking. Ideally, follow-up in a multidisciplinary vascular anomalies center is beneficial.

TELANGIECTASIA

Though not true CMs, telangiectasias can present in infancy or early childhood and often persist. They are usually composed of small, punctate linear vessels distributed in either a segmental, unilateral nevoid, or diffuse pattern. A variety of telangiectatic skin lesions have been described. Most are absent at birth, often developing in childhood. A pale halo of vasoconstriction may surround small telangiectasias. Toddlers and young children sometimes develop so-called spider angiomas comprised of a brightly erythematous central punctum with radiating ‘spider-like’ telangiectasias. They are usually located on sun-exposed areas. Risk factors include fair skin and a history of minor skin injury at the site. These may disappear spontaneously over years, or persist. Fine telangiectasias are occasionally present on the cheeks of normal young children, but extensive telangiectasias in the photo-distribution should prompt consideration of conditions with photosensitivity such as Rothmund–Thomson syndrome. Persistent telangiectasias can also be seen as a sequela of neonatal lupus. The facial telangiectasias associated with hereditary hemorrhagic telangiectasia (HHT) and ataxia–telangiectasia usually present later in life.

Venous malformations

Venous malformations (VM) are slow-flow vascular malformations that are usually evident at birth. They may involve skin, mucosa, subcutaneous tissues, muscle and rarely bone. They are composed of ill-defined venous channels with irregularly attenuated walls, focally lacking smooth muscle cells, permeating the skin and adnexal structures. Glomuvenous malformation (GVM) is a subtype of VM composed of anomalous venous channels lined by glomus cells, which are actin positive and do not lack smooth muscle. Glomus cells have a characteristic appearance on histopathology.

Pathogenesis

VMs are sporadic in the majority of cases, but, familial cases of both VM and (more often) GVM occur. The genetic basis for familial VMs (VMCM syndrome, see below) and GVM are now known. The mutated gene in familial VMCM syndrome maps to chromosome 9p17; and is an activating mutation in the kinase domain of the receptor tyrosine kinase Tie2.³⁶ Sporadic Tie2 mutations are also found in 50% of sporadic VMs.³⁷ GVM can be either a sporadic or an autosomal dominant condition, linked to mutations in the glomulin gene (mapping to 1p21–p22). Unlike VMs, far more cases of GVM are familial (approx. 64%).^{38,39}

Cutaneous findings

At birth, the majority of VM are subtle, bluish, ill-defined, compressible plaques or nodules. Rarely, a bulky venous mass is observed in the neonatal period (Fig. 22.5). VMs may be diffuse or localized. Affected skin and mucous membranes are typically blue with normal skin temperature, without a thrill or bruit. Lesions swell when dependent or with crying. In many cases, the blue-hued cutaneous component heralds involvement of deeper structures. Local venous thromboses can lead to the formation of phleboliths, which can be tender when palpated and are visible on radiographs as round calcifications.

Glomuvenous malformations (GVM; formerly called ‘glomangioma’) may be solitary or multiple, and may be localized or involve a larger territory of skin (Fig. 22.6). They are often bluish to purple, cobblestoned or plaque-like in appearance. During childhood, they typically acquire a deeper blue hue and thicken, and become tender when palpated. Congenital plaque-like GVMs are usually pink at birth, with noticeable thickening and change in color to blue-purple during childhood. These plaque-like GVMs may arise sporadically, or occur as a manifestation of autosomal dominant GVM. Other family members



Figure 22.5 Small venous malformation of the finger, with swelling and blue nodularity.



Figure 22.6 Extensive glomuvenous malformation on the chest and arms in an infant with + glomulin mutation. (Courtesy of Ilona Frieden.)

TABLE
22.3

Hereditary lymphedema syndromes

Syndrome	Genetic basis	Clinical features
Primary congenital lymphedema (Nonne–Milroy disease)	Autosomal dominant Mutations in <i>VEGFR3</i>	Congenital lymphedema of lower limbs, mainly below knees. Slow to progress. Can be associated with hydrocele, enlarged leg veins and recurrent cellulitis
Pubertal onset lymphedema (Meige disease, lymphedema distichiasis syndrome)	Mutations in <i>FOXC2</i>	Pubertal onset, most common type of primary lymphedema. Can be associated with distichiasis, ptosis, yellow nails, syndactyly, cleft palate and cardiac septal defects
Hypotrichosis–Lymphedema–Telangiectasia syndrome	Autosomal dominant and recessive forms reported mutations in <i>SOX18</i>	Lymphedema, sparse hair, cutaneous telangiectasias
Hennekam syndrome (generalized lymphatic dysplasia, GLD)	Autosomal recessive Mutations in <i>CCBE1</i> in some cases	Lymphedema, intestinal lymphangiectasia, protein-losing enteropathy, developmental delay, multiorgan involvement

may have smaller, blue vascular lesions scattered over the skin, increasing in number with age.³⁸

Extracutaneous findings

In addition to skin and mucosal involvement, VM can also involve deeper soft tissues, muscles, joints, and in severe cases, visceral sites such as the abdomen and pelvis. A majority of patients with extensive VMs develop a chronic localized intravascular coagulopathy (LIC), which is distinct from Kasabach–Merritt phenomenon (KMP). VM associated LIC can result in either thrombosis (with pain and phlebolith formation) or bleeding, and persists throughout life. It differs from KMP because the primary process is one of ongoing clotting, with consumption of clotting factors, low fibrinogen and elevated D-dimers, but without the marked thrombocytopenia of KMP.^{40,41} Large and intramuscular VMs are more likely to have associated VM-LIC. Pain is a common complaint either due to phlebolith formation or often in larger extremity lesions.⁴² ‘Blue rubber bleb nevus’ syndrome, the association of multiple cutaneous venous malformations with gastrointestinal and other internal lesions, is discussed later in this chapter. Some patients with VM experience worsening of symptoms during puberty or in pregnancy. In contrast to VMs, GVMs are typically localized to the skin and soft tissues without mucosal or intramuscular involvement. GVMs are not associated with LIC.

Diagnosis

The diagnosis is usually established on the basis of clinical features. Imaging modalities including ultrasonography, Doppler, MRI, and CT scans are useful for evaluating the extent of involvement.⁴³ The finding of associated LIC and specifically elevated D-dimer levels, can help confirm the diagnosis of VM in uncertain cases.⁴⁴ Apart from helping to confirm the diagnosis, the decision to image early in infancy depends on whether functional problems are present or early treatments are planned. Many VMs, however, especially larger ones, eventually do require imaging studies, and MRI with contrast is the best study to delineate disease. A number of radiologic classification schema have been proposed and may predict response to treatment, with smaller and more localized lesions being more amenable to sclerotherapy.⁴⁵ In individuals with craniofacial VMs, it is advisable to image the brain: developmental venous anomalies (DVA) in the brain are more common in patients with craniofacial VMs than in the general population (25% vs 0.5%).⁴⁶ DVAs are uncommon trajectories of the brain’s venous

drainage and pose little risk of cerebral hemorrhage, but documenting their presence can help avoid misdiagnosis of a more worrisome condition later in life. Histopathology can also help to confirm the diagnosis when uncertainty is present and/or to distinguish between VM and GVM.

Differential diagnosis

Extensive VMs in a leg or an arm and adjacent trunk must be differentiated from Klippel–Trenaunay and other overgrowth syndromes, as management and prognosis is variable (see Table 22.4). Sinus pericranii should be considered in the differential diagnosis of a VM located on the central forehead. This presents as a bluish, nonpulsating mass that is usually congenital and quickly expands when the patient puts their head in a dependent position or with crying. Sinus pericranii represents a direct communication between superficial veins and intracranial venous sinuses through a bony defect. It is best imaged using CT with bone windows.

Course

Venous malformations tend to enlarge and become more symptomatic with time. Their clinical course and complications depend on anatomic location, with differing problems in the craniofacial area, trunk, and limbs.⁴¹ The cheek, lip and tongue are common locations for craniofacial VMs, and there is sometimes deep extension to the temporal and orbital areas. Swelling is noted with dependency and activity. Over time, the VM may progressively distort the facial features and mold the underlying developing bones, which can result in deformities such as an open bite or enlargement of the orbit. Extensive retropharyngeal involvement can result in obstructive sleep apnea, occasionally even in young children. VMs located on the trunk and limbs may involve skin, skeletal muscles, joints, and bones, often causing pain. During infancy and early childhood, the skin component of the VM expands and becomes deep blue. However, the deeper component may remain undiagnosed until it becomes symptomatic. Swelling, functional impairment, and limited joint motion occur when the child becomes older and more active, especially if playing sports. VM-LIC associated with large and intramuscular VM can manifest as early as the neonatal period.

Management

Due to the heterogeneity of VMs and the clinical and radiologic diagnostic overlap with other vascular anomalies, multidisciplinary

management is recommended. VMs are reported to comprise up to 40% of referrals to vascular anomalies centers.⁴⁷ VMs can be treated with many different modalities including sclerotherapy, excision, endovenous laser ablation, cutaneous laser ablation or a combination of these modalities. Sclerotherapy has emerged as the mainstay of treatment for VMs, followed by surgical excision. The decision regarding when to treat is usually based on whether there is significant functional impairment or disfigurement. Sclerotherapy involves the introduction of an endothelial-cell cidal sclerosant into the vascular spaces of the malformation.⁴⁸

Several different sclerosants can be used, including ethanol or sodium tetradecyl sulfate. Complications of sclerotherapy include tissue necrosis, nerve palsies, hemoglobinuria and oliguria.⁴⁹ Surgical management can be most helpful in small or localized lesions. A combination of sclerotherapy followed by surgical debulking is often used in large or complex cases. In craniofacial lesions, therapy is aimed at preventing distortion of facial anatomy, limiting bone deformity, open bite or shift of the dental midline, lip expansion, and displacement of the lip commissures.^{50,51} MRI and ultrasound features may be especially helpful in determining optimal management.⁵¹ Multiple treatments are often required over years. Laser or radiofrequency ablation are occasionally helpful. Conservative therapy with compression should be initiated early on and is even encouraged from infancy in diffuse extremity VMs. Compression increases comfort, limits swelling, and improves coagulopathy. Compression is less useful for intramuscular VMs and may exacerbate pain.

Evaluation of large VMs includes assessment for, and possibly treatment of, VM-LIC. D-dimer levels should be obtained periodically to assess the extent of coagulopathy. Treatment with low-dose aspirin can be a helpful adjunct to conservative therapy in some cases. Low molecular weight heparin (LMWH) has been found to be useful in patients with chronic VM-LIC during episodes of exacerbation (thrombosis, pain) or before and after planned procedures such as sclerotherapy or surgical excision, to prevent thrombosis and/or control intraoperative hemorrhage.⁵² In patients with a history of thromboembolic events or in those with high risk, large and/or combined malformations, placement of an inferior or superior vena cava filter may help prevent pulmonary embolus.⁵³

Lymphatic malformations

Lymphatic malformations (LMs) are slow-flow vascular anomalies known in much of the literature as 'lymphangioma'. They can be macrocystic, microcystic, combined or very rarely generalized. LMs arise in a sporadic manner and can also be syndromic.

Pathogenesis

The etiology of LMs is still unknown. LMs arise in a sporadic manner and no associated genetic basis has yet been discovered. This may suggest that a genetic cause is likely related to somatic mutations, which, if occurring within the germline, would be incompatible with life.⁵⁴ This is in contrast to primary lymphedema, where several genetic mutations leading to specific lymphedema syndromes have been discovered and have improved our understanding of the molecular pathways involved in lymphangiogenesis.⁵⁵ In primary lymphedema,

defective lymphatic drainage leads to accumulation of lymphatic fluid in the interstitial space (Fig. 22.7).

Several forms of lymphedema are known, including familial congenital lymphedema, Nonne–Milroy syndrome, Meige disease, and Hennekam syndrome, summarized in Table 22.3.

Cutaneous findings

Macrocystic LMs are usually visible at birth and are commonly diagnosed by prenatal ultrasound investigation. They occur more commonly in the neck and axilla, where they are often referred to as cystic hygroma (Fig. 22.8).⁵⁶ The detection in utero of some huge LMs of the neck, axilla, and thoracic area may lead to a discussion about terminating the pregnancy, as the prognosis is poor. Microcystic LMs can infiltrate diffusely throughout the dermis. Clear or hemorrhagic vesicles (so-called 'lymphangioma circumscriptum'), which may intermittently leak lymphatic fluid, may be visible on the surface of the lesion. Severe combined LMs may also occur on the trunk and limbs.⁵⁷

Extracutaneous findings

Cervicofacial LMs involving the tongue and floor of the mouth will interfere with normal development of the jaw and create an open bite deformity. The most severe forms of combined



Figure 22.7 Congenital lymphedema. (Courtesy of Angela Hernandez-Martin, MD.)



Figure 22.8 Large thoracic lymphatic malformation ('cystic hygroma') present at birth.



Figure 22.9 Large lymphatic malformation of the face with both microcystic and macrocystic elements involving the skin and mucosa.

micro/macrocystic LMs, which are more common on the head and neck, can cause life-threatening airway disease and other functional problems in the neonate (Fig. 22.9). Intraoral involvement also causes drainage of serosanguineous lymphatic fluid, aggressive caries, and loss of teeth. Involvement of the mandible with ensuing overgrowth is present in about 40% of these patients.^{58,59} Extra- and intraconal orbital LM occurs in association with eyelid LM; this uncommon location causes severe complications including disfigurement, bleeding, infection, proptosis, and visual loss.⁶⁰ Severe cervicofacial LMs, usually the combined micro/macrocystic type, involving the hypopharynx and larynx, the tongue and the floor of the mouth, can cause airway and esophageal obstruction requiring nasogastric tube feeding and emergency tracheotomy in the newborn.⁶¹ Of 31 cases with such severe involvement, 58% required tracheostomy in infancy and one-third could not be decannulated.⁵⁹ Visceral LMs, intrathoracic or abdominal, are less common, representing about one-tenth of cases. LMs are more susceptible to bacterial infections, and recurrent cellulitis can be a complication.

Diagnosis

The diagnosis is established either clinically or using CT, MRI, or ultrasound. Fluid aspiration and analysis may be helpful because a number of neonatal growths, including some malignant tumors, can present with large cyst-like swellings.⁶² Histologically, lymphatic vessels or cysts have thin walls and lumina appear empty. Several positive immunohistochemical markers of lymphatic vessels have been identified, including LYVE-1, VEGFR-3 and D2-40, and can help to differentiate LM from other vascular anomalies.

Treatment

Lymphatic malformations are benign and treatment is usually directed at managing complications or attempting to restore anatomy. Conservative measures include observation, prophylactic antibiotics when infection is a concern, and in the case of primary lymphedema, compression. Sclerotherapy has emerged

as an important treatment for LMs, and can be done early, even in the neonatal period. A variety of sclerosing agents have been used, including doxycycline, ethanol, bleomycin, OK-432 and STS. Macrocystic LMs respond very well to sclerotherapy. Surgical resection is another therapeutic option for macrocystic LMs, as well as for microcystic and combined types, but recurrences and complications such as seroma or chronic lymphatic leakage may occur.^{58–60,63,64} Radiofrequency ablation can be helpful in the management of LMs, most commonly for the lips and tongue to help decrease chronic leakage and bleeding.^{65,66}

A multidisciplinary approach is required for complex LMs.⁵⁹

Arteriovenous malformations

Arteriovenous malformations (AVMs) are fast-flow anomalies that most commonly arise in the head and neck area. Macular erythema mimicking a PWS, with increased local warmth, and subtle skin thickening can be clues to the diagnosis.

Pathogenesis

Arteriovenous malformations arise due to errors in vascular development, which occur during embryogenesis. AVMs represent direct shunting from the arterial to the venous system due to the absence of an intervening capillary bed. Recently, the genetic basis for familial types of AVM has been discovered. Mutations in *RASA1* have been found in individuals with AVM of the extremity (Parkes Weber syndrome) and in CM AVM syndrome (see below for further discussion on Parkes Weber syndrome), vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies caused by *RASA1* mutations.⁹ Other mutations associated with AVMs or AVM variants include endoglin, which gives rise to hereditary hemorrhagic telangiectasia syndrome (HHT) and *PTEN* as seen in high flow lesions of the *PTEN* hamartoma tumor syndrome (see below).

Cutaneous findings

Most commonly, AVMs present as a pink vascular stain on the skin, mimicking port-wine stain. They are often located on the head and neck, the nose and central face/lip are common locations as is the ear (Fig. 22.10). As mentioned above, lesions are warm and may have a thrill or a bruit. AVMs may develop pyogenic granulomas within them that bleed and may need to be excised or treated with laser ablation.⁶⁷ Any patient who presents with small, multifocal lesions that resemble PWS but demonstrate high flow on Doppler examination should receive a workup for CM AVM syndrome (see below). Lesions may become thicker, more nodular and darker in color with time. AVMs often progress during puberty or with trauma.

Extracutaneous findings

AVMs can be life-threatening lesions that worsen over time. Complications include disfigurement, pain, bony erosion, hemorrhage, and even death. Large AVMs may have associated high-output heart failure at birth or later in life, requiring intervention.

Diagnosis

Most AVMs can be diagnosed based on their natural history and physical examination characteristics. They may not be obvious at birth, most commonly lesions mimic port-wine stain, but unlike PWS, AVMs expand through childhood. In general,



Figure 22.10 (A) A 5-day-old neonate with a midfacial quiescent arteriovenous malformation that subsequently worsened and proved to be part of a Bonnet–Dechaume–Blanc syndrome. (B) The same child at 8 years of age.

AVMs are warm, a bruit may be audible, and a thrill may be palpable. An actual vascular mass with tense draining veins, a thrill, and a bruit is uncommon for AVM in a newborn, and may represent a congenital hemangioma (see [Chapter 21](#)). The Schobinger Classification of AVMs divides the presentation into four stages based on severity and associated findings: Stage I, lesions are quiescent; Stage II, AVMs have expanded and a thrill or bruit is palpable; Stage III, AVM destruction occurs and lesions can lead to ulceration, bleeding and pain; and Stage IV AVMs are associated with cardiac compromise.⁶⁸

Color Doppler ultrasonography as well as MR with MR angiography may be helpful in diagnosis, as well as delineating the extent of disease. Angiography is sometimes done to aid in diagnosis or in preparation for embolization or resection. In contrast to VMs, AVMs are not known to be associated with LIC.

Management

Early on, conservative observation may be the best course for Stage I and II AVMs, as interventions may lead to enlargement or worsening of the lesions secondary to trauma. In more advanced malformations, where there are complications or functional compromise, embolization is usually the first-line treatment. Embolization can also be done prior to a planned surgical resection.⁶⁹ Embolization involves the delivery of an embolic agent, usually ethanol, onyx, polyvinyl alcohol or coils, into the AVM in an attempt to block the blood flow and reduce shunting.⁷⁰ Embolization is considered a palliative measure, as there is no cure for AVMs. Surgical management of AVMs should be performed with caution as exacerbation or recurrences are common and any resulting deformity may not be cosmetically acceptable.⁷⁰

Combined malformations

Vascular malformations occur most commonly as described above, manifesting as CM, VM, LM, or AVM. However, any combination of malformed vessels may occur together and a

number of combined malformations are well recognized. In the past, many of these disorders were named eponymously, which sometimes leads to confusion in the diagnosis of these rare entities. Classification based on the vessel type predominant in the malformation may be a better way to distinguish them. Nonetheless, many of the eponyms persist and are widely used. Many of the combined vascular malformations are associated with overgrowth of the affected areas of the body ([Table 22.4](#)). Most commonly, capillary-lymphatic-venous malformation (CLVM) is described in association with various conditions including Klippel–Trenaunay and CLOVES. Combined fast-flow malformations such as capillary arteriovenous malformation (CAVM) and capillary arteriovenous fistulae (CAVF) are also described and are the main presenting feature of Parkes Weber syndrome. Some CAVM patients have underlying RASA1 mutations or CM-AVM syndrome (see below).

Syndromes associated with vascular malformations

The syndromes described below are associated with various vascular anomalies. We have elected to group them based on the most prominent or characteristic cutaneous vascular anomaly as this is often the first presenting sign of the disorder. Most of these malformations are evident at birth or become apparent in infancy or early childhood. In some cases, the genetic basis for the syndrome is known.

SYNDROMES ASSOCIATED WITH CAPILLARY MALFORMATIONS

Sturge–Weber syndrome

The classic triad in Sturge–Weber syndrome (SWS) includes the association of a facial port-wine stain, invariably involving V1 (although it may be more extensive) ([Fig. 22.2](#)), ipsilateral eye abnormalities (choroidal vascular anomalies, increased ocular pressure, buphthalmos, and glaucoma), and leptomeningeal

TABLE
22.4

Vascular malformation syndromes associated with overgrowth

Syndrome	Genetic basis	Cutaneous features, vascular malformation	Extracutaneous features
Beckwith–Wiedemann	Chrom 11p Genomic imprinting Contiguous gene duplication	Nevus simplex/CM of philtrum or glabella	Hemihypertrophy, visceromegaly, macroglossia, omphalocele, Wilms tumor
CLOVES	PIK3CA	Malformations associated: CM, CLVM, LM, AVM Epidermal nevi Lipomas	Truncal lipomatosis, skeletal anomalies, macrodactyly, sandal gap deformity, risk for pulmonary embolus, Wilms tumor
Klippel–Trenaunay	Unknown	CLVM, CM, CVM Typical geographic morphology of malformation	Overgrowth or undergrowth of affected limb, leg length discrepancy, contractures, coagulopathy, risk for pulmonary embolus
MCAP	PIK3CA, AKT1	CM	Megalencephaly, hemihypertrophy/asymmetric overgrowth, developmental delay, seizures, hypotonia, brain malformations, polymicrogyria
SOLAMEN	PTEN	AVM, LM Epidermal nevus collagenomas	Segmental overgrowth, lipomatosis
Proteus	AKT1	Slow-flow malformations: CM, CLVM, LM Connective tissue nevi	Progressive overgrowth, risk for pulmonary embolus

and brain abnormalities (leptomeningeal vascular malformation, calcifications, cerebral atrophy, enlarged choroid plexus, and developmental venous anomalies in the brain). The risk of SWS with V1 PWS alone is variably reported but is approximately 10%. The risk increases to $\geq 25\%$ with either bilateral V1 or concurrent V1, V2, and V3 involvement. Patients with V2 or V3 PWS alone without involvement of the V1 skin are not at risk for SWS. However, individual anatomic variations in the distribution of V1 and V2 at the internal or external canthus of the eye may pose difficulties in determining whether a port-wine stain involves V1, with its associated risk of SWS (Fig. 22.11). The possibility of SWS should be considered in any infant with a PWS that includes the V1 distribution.⁷¹

SWS can cause significant medical and ophthalmologic problems. Consequences of intracranial vascular anomalies include seizures, headaches (including migraines), spastic hemiparesis, visual field defects, cognitive impairment and behavioral disorders including attention deficit disorder. Transient ischemic attacks and strokes may also occur in some patients. An increased prevalence of growth hormone deficiency and hypothyroidism is described in patients with SWS, so at-risk individuals need to be assessed for these potential complications.⁷² Potential visual loss via acute or chronic glaucoma requires ongoing ophthalmologic follow-up throughout a patient's lifetime. Even an individual who has a V1 PWS without CNS findings should have periodic ophthalmologic evaluations throughout their lifetime.

The pathogenesis of SWS has recently been attributed to somatic activating mutations in *GNAQ*.⁹ The three mesectodermal tissues involved (the nasofrontal skin known as V1 skin, the ocular choroid, and the leptomeninges) have a common origin in the anterior neural primordium and a somatic mutation arising during development has been hypothesized. Neuroimaging consisting of MRI with gadolinium enhancement may be helpful in making an early diagnosis, but can be normal in some cases. Early subtle changes on standard MRI can include an

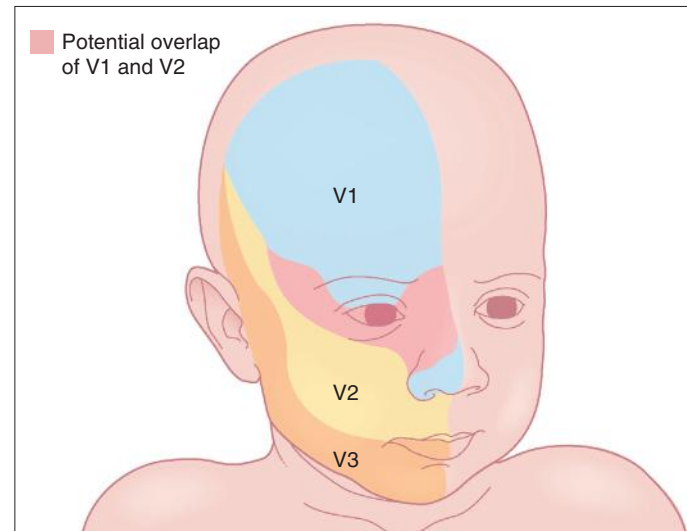


Figure 22.11 Anatomic diagram of branches of the trigeminal nerve. The pink area denotes the potential overlap of V1 and V2. (Adapted from Enjolras O, Riche MC, Merland JJ. Facial port-wine stains and Sturge–Weber Syndrome. *Pediatrics* 1985; 76:48–51).

enlarged choroid plexus or a pattern of local accelerated myelination. Typical neuroimaging changes include visualization of the pial vascular malformation, cerebral atrophy, and calcifications of the leptomeninges, the abnormal cortex and the underlying white matter.⁷³ Newer MRI modalities such as susceptibility-weighted imaging may prove useful in detecting abnormalities earlier in life. In most patients, the first seizures in SWS occur before 2 years of age but may arise later in life. The progressive nature of SWS has been demonstrated using functional neuroimaging tools, with hyperperfusion noted prior to the development of seizures, followed by

BOX 22.1 MANAGEMENT OF STURGE-WEBER SYNDROME

- Regular ophthalmologic evaluation
- Treatment of glaucoma (surgical and/or medical)
- Neurologic evaluation
- Optimal control of seizures
- Laser treatment of PWS (after seizure disorder is controlled or prophylactically treated)
- Management of maxilla overgrowth, open bite deformity, and gingival hyperplasia when present

Patient and family support:

The Sturge–Weber Foundation. Contact information:

International:

PO Box 418, Mount Freedom, NJ 07970, USA

Phone: 800-627-5482; E-mail: swf@sturge-weber.org;

URL: www.sturge-weber.org

Canada:

1960 Prairie Avenue, Port Coquitlam, BC V3B 1V4, Canada

Phone/Fax: 604-942-9209; E-mail: sturge-weber@shaw.ca;

URL: www.sturge-weber.ca

UK and Europe:

See: www.sturge-weber.org

hypoperfusion with decreased glucose utilization after the onset of seizures.^{74,75} Newer noninvasive tools including quantitative electroencephalography and transcranial Doppler are under investigation and may prove promising for the evaluation and management of children with SWS.⁷²

Careful follow-up is recommended for newborns with an at-risk V1 PWS. Although controversial, some pediatric neurologists believe that prophylactic anti-seizure medications or low dose aspirin regimens are worth considering for at-risk infants.^{76,77} Therapeutic management of SWS (Box 22.1) is often characterized by a lifelong struggle to preserve vision, motor and psychomotor development, and to ameliorate disfigurement.

Macrocephaly capillary malformation syndrome (megalencephaly capillary malformation polymicrogyria syndrome)

Macrocephaly capillary malformation syndrome (MCM/MCAP) was formerly known as macrocephaly CMTC. However, the most commonly associated vascular anomalies are a persistent nevus simplex or typical CM/PWS (not CMTC) and the diagnostic criteria for this condition were revised to reflect this.^{78,79} MCM/MCAP is associated with megalencephaly, developmental delay, brain and body asymmetry, capillary malformations, digital anomalies (syndactyly, polydactyly), and brain malformations; characteristically, polymicrogyria. Other features include seizures, developmental delay, hydrocephalus, and joint laxity. Recently, the genetic basis for this condition has been identified. Affected individuals were found to harbor mutations in the AKT3, PIK3CA or PIK3R2 genes.⁸⁰ MCM/MCAP is a heterogeneous overgrowth syndrome, most commonly patients present with macrocephaly and cutaneous CMs. The associated capillary stain is most commonly located on the central face (philtrum and glabella) but can be seen on any area of the body. As in all overgrowth syndromes, there is a possibility of increased risk for Wilms tumor – many experts recommend serial abdominal ultrasounds in infancy and early childhood.

Beckwith–Wiedemann syndrome

Beckwith–Wiedemann syndrome (BWS) is a pediatric overgrowth disorder that carries an increased risk for malignancy, specifically Wilms tumor. BWS can present antenatally with visceromegaly on prenatal ultrasonography. It is associated with persistent nevus simplex or capillary malformation of the mid-forehead. Other findings include overgrowth of tissues and organs, macroglossia, and abdominal wall defects, usually omphalocele. High birthweight, hemihypertrophy, and neonatal hypoglycemia are also reported. Intelligence is usually not impaired.

The genetic basis of BWS is complex and several different modes of inheritance are possible. Inheritance can be via autosomal dominant, contiguous gene duplication or genomic imprinting. Chromosome 11p is implicated in several of these inheritance modes.⁸¹

Nova syndrome

Nova syndrome is a familial disorder in which a congenital glabellar capillary stain occurs in association with neurologic malformations, including Dandy–Walker malformation, hydrocephalus, cerebellar vermis agenesis, and mega cisterna magna.

Phakomatosis pigmentovascularis

Phakomatosis pigmentovascularis (PPV) is a term used to describe the association of cutaneous pigmentary and vascular anomalies. Five types with two subtypes per group are classically described. An alternate classification uses descriptive terminology to highlight the cutaneous features (Table 22.2, Fig. 22.4). Capillary malformations are described in types I–IV and cutis marmorata telangiectatica congenita in type V. The pigmentary anomalies include blue-gray macules/patches (dermal melanocytosis), nevus spilus and epidermal nevi which are darkly pigmented. Nevus anemicus is also reported. PPV has been described in association with other vascular anomalies including Klippel–Trenaunay syndrome and Sturge–Weber syndrome.^{82,83}

SYNDROMES ASSOCIATED WITH VENOUS MALFORMATIONS

Venous malformations cutaneous and mucosal (VMCM), glomuvenous malformations and blue rubber bleb nevus syndrome (Bean syndrome)

Somatic and familial venous malformations arise due to mutations in the Tie2 gene, a tyrosine kinase receptor involved in angiogenesis.³⁷ In the familial VMCM syndrome, the malformations are typically small and superficial, located mainly in the skin and mucosa, though they can be found invading skeletal muscle and have been reported both in the GI tract and the brain. Since the lesions are usually small and asymptomatic, family members may be unaware of the syndrome, even though it is inherited in an autosomal dominant pattern. Lesions can be present early on and individuals can acquire more VMs with time. This is due to the mode of inheritance, whereby a second mutation within the Tie2 gene leads to the development of more lesions, analogous to Knudson's two-hit hypothesis theory postulated for retinoblastoma.⁸⁴

Familial glomuvenous malformations are usually inherited in an autosomal dominant manner, but can also be sporadic. Mutations in the glomulin gene have been identified in affected

patients. As described above, GVM often resemble VM clinically. They can be small or large/segmental in their appearance (Fig. 22.6). They are bluish to purple, cobblestoned in appearance and often painful on palpation. There is great heterogeneity among affected family members, which suggests that a single mutation in the glomulin gene is not enough to produce the lesion, thus as in VMCM, a second post-zygotic mutation in the unaffected allele is required for the lesion to develop.

Blue rubber bleb nevus syndrome (BRBNS) is a rare congenital disorder in which patients present with multifocal venous malformations in the skin, soft tissue, and gastrointestinal tract.⁸⁵ The associated VMs are typically small black-blue papules and skin-colored subcutaneous nodules that often involve the palms and soles. GI bleeding occurs in infancy or early childhood and can lead to chronic anemia necessitating transfusion. Lesions are commonly observed in the small bowel and colon. There is much confusion in the literature regarding the diagnosis of BRBNS, as other familial VM syndromes such as VMCM and GVM can present with similar-appearing lesions. BRBNS is less common than the other familial VM syndromes, and it is thought that GI involvement and associated bleeding are unique to BRBNS. Surgical management of patients with chronic GI bleeding and resultant anemia has been reported as a successful intervention.⁸⁶ The differential diagnosis of BRBNS in the newborn period also includes multifocal infantile hemangiomas and multifocal lymphangioendotheliomatosis (see Chapter 21).

Maffucci syndrome

Maffucci syndrome (MS) is a rare sporadic syndrome characterized by vascular lesions of the skin and multiple bone tumors. This form of enchondromatosis is associated with spindle cell hemangioma, begins in childhood and worsens with maturity. Congenital forms occur and disease presents in 25% of cases by the first year of life.⁸⁷ The skin lesions clinically resemble venous malformations, are nodular, develop slowly, and are rare in infancy. Although they have features of slow-flow venous anomalies – phleboliths, hypersignal on signal-enhanced T₂ sequences with MRI – histologic examination reveals a spindle cell hemangioma, in addition to malformed venous channels.⁴ Enchondromas are benign cartilage-forming tumors within the medullary cavity of the bone. These tumors are identical to those present in another form of multiple enchondromatosis, Ollier disease. They involve both the metaphyses and the diaphyses, and may cause bony distortion, fragility, and shortening of an affected limb. The hands and feet are involved in 90% of patients. Cranial enchondromas result in severe neuro-ophthalmologic consequences. Over time, enchondromas may develop malignant transformation. Somatic mosaic *IDH1* and *IDH2* mutations are associated with the lesions in both Ollier disease and MS.⁸⁸

Cutis marmorata telangiectatica congenita

Cutis marmorata telangiectatica congenita (CMTC) is a form of vascular malformation with a distinctive reticulated pattern. Most cases are sporadic. A female predominance is reported in some cases series, while others show no difference in incidence among genders.^{89,90} CMTC can be confined to a small area, have a regional distribution, or more diffuse skin involvement. At birth, a reticulated purple network is noted. The skin is streaked with linear and patchy vascular lesions intermingled with telangiectasia. Within affected areas there are often focal areas of



Figure 22.12 Neonate with cutis marmorata telangiectatica congenita (CMTC) on the arm.

atrophy and/or ulceration, even during the neonatal period (Fig. 22.12). These changes are often most prominent over the limbs. This conspicuous atrophic reticulate pattern differs from physiologic cutis marmorata, a normal finding in newborns, in that the pattern is coarse and less regular. CMTC may be associated with port-wine stains, which can become more apparent with maturity as the reticulate lesions fade. CMTC may improve with age, but rarely disappears completely with areas of atrophy often persisting. Ulcerations may continue to arise during infancy and childhood, particularly in areas overlying the joints, resulting in scaly areas of scarring.

Localized or regional CMTC with involvement of one or two areas of skin (most often the extremities) is more common than the diffuse type, but because of its generally benign course is likely less frequently reported in the literature. A difference in limb girth is common, and the affected limb may have a thinner, pseudo-‘athletic’ appearance compared with the normal extremity as a result of having less fat or diminished muscles and bones. Subsequent growth is usually proportional to the original degree of limb asymmetry.⁹¹ Multiple abnormalities have been reported in association with CMTC, however, care should be taken when reviewing older case series, since cases of macrocephaly CM syndrome associated with a reticulated capillary malformation and not true CMTC, may have been included. The most frequently described associated anomaly in many case series is body asymmetry. Other reported associated anomalies include musculoskeletal anomalies, vascular abnormalities including co-existing capillary malformations/PWS, arterial stenosis and cardiac defects. CMTC, syndactyly, cardiac defects and alopecia are features of Adams Oliver syndrome.⁹² Less frequently reported anomalies include brain and spinal cord defects, glaucoma and other ocular anomalies, imperforate anus, abnormal genitalia, dystrophic teeth, congenital hypothyroidism, stenosing tendonitis, and others.^{89,91,93–96,90}

The differential diagnosis of CMTC includes macrocephaly CM syndrome, which is discussed above, and persistent true cutis marmorata. Neonatal lupus can be associated with extensive livedo reticularis, telangiectasia, and atrophic striae, and mimics CMTC.⁹⁷ Less generalized PWS with a blotchy reticulated quality are also sometimes mistaken for CMTC. The residual, persistent, reticulate vascular lesions of CMTC respond poorly to pulsed dye laser treatments and can be associated with



Figure 22.13 Infant with early verrucous hemangioma of the lower leg.

a greater risk of scarring than is usually associated with this mode of therapy. Associated port-wine stains, however, are amenable to PDL therapy. Management of extracutaneous associated abnormalities is directed at specific signs or symptoms. Infants with CMTC located in a distribution similar to the port-wine stain of Sturge–Weber syndrome are at higher risk for CNS and ophthalmologic complications and require evaluation.

Verrucous hemangioma and angiokeratoma circumscriptum

Verrucous hemangioma (VH) is a rare congenital vascular anomaly which has historically been classified as a vascular malformation but shows immunohistochemical features of both a vascular tumor and vascular malformation.^{98,99} VH presents in infancy and is typically located on the lower extremities but may arise at other sites (Fig. 22.13). It may be a single lesion or grouped. Initially, there are blue to purple soft compressible lesions that develop overlying hyperkeratosis and bleeding over time. In its early stages VH may mimic an infantile hemangioma, venous malformation or combined venous lymphatic malformation. The lesions persist and do not involute. As hyperkeratosis develops, the lesion may mimic angiokeratoma, and capillary-lymphatic-venous malformation or even a pigmented/melanocytic lesion.

Angiokeratoma circumscriptum is another rare congenital vascular anomaly which often occurs on the lower extremities. At birth, it may present as pink-red patches and become increasingly hyperkeratotic with age.^{99–101} Histopathologic evaluation of VH reveals verrucous hyperplasia of the epidermis overlying a vascular lesion composed of small sized vessels separated by fibrous and adipose tissue. There is extension into the subcutis and in some cases the fascia. This is particularly important when undertaking removal, since wide excision is required in order to prevent recurrence. These features help to differentiate them from angiokeratoma, which may be congenital or appear later in childhood and are usually small and superficial. Immunohistochemical analysis can reveal focal immunoreactivity for GLUT1 (a marker that is typically seen in infantile hemangiomas)⁹⁹ and negative for staining for lymphatic differentiation and Wilms Tumor 1 transcription factor (WT1). WT1 is typically positive in vascular tumors and negative in vascular



Figure 22.14 Infant with CM-AVM syndrome and a typical-appearing CM-AVM stain of the left chest. This lesion demonstrates high flow on Doppler evaluation, differentiating it from classic CM. In CM-AVM syndrome the lesions tend to be multifocal with more arising over time.

malformations.^{102,103} The diagnosis of this rare vascular anomaly is best established with clinicopathologic correlation.

SYNDROMES ASSOCIATED WITH ARTERIOVENOUS MALFORMATIONS

Capillary malformation-arteriovenous malformation syndrome

The capillary malformation-arteriovenous malformation (CM-AVM) syndrome¹⁰⁴ was first described in 2003. It is characterized by the combination of congenital and acquired capillary malformations and an AVM of the soft tissue or central nervous system. Infants are often born with multiple pink patches, which may mimic a hemangioma precursor, or a larger CM (Fig. 22.14). The pink patches often increase in number with maturity. CM-AVM is inherited as an autosomal dominant trait, with wide expressivity. Some affected family members may have symptomatic AVMs, whereas others exhibit only small, pink patches, however the true incidence of underlying AVM is not fully understood because not all individuals have undergone complete evaluation. In the families that have been evaluated, approximately two-thirds of individuals will have the AVM located in the soft tissue and one-third in the central nervous system. In many patients, the AVM will underlie the largest CM. Parkes Weber syndrome (see below) is one of the ways CM-AVM will present and may do so in the neonatal period with an enlarged limb, overlying CM and a underlying fast-flow AVM or AVF, or vein of Galen malformation which can lead to cardiac compromise. The disease is caused by mutations of *RASA1*. Genetic testing is available and evaluation of the index patient and family members is recommended, as these skin lesions may be a marker for CNS AVM risk.^{9,105}

Wyburn–Mason, Bonnet–Dechaume–Blanc, and Brégaat syndromes

These rare syndromes are characterized by arteriovenous malformations in the craniofacial area with fast-flow vascular anomalies in the skin (midline or hemifacial), orbit, retina, and brain (thalamus, hypothalamus and optic chiasm). These

eponyms are now considered to be synonymous. In infancy, the cutaneous AVM commonly mimics a facial port-wine stain, although it is usually fainter and less well-demarcated than PWS (Fig. 22.10). It is warm on palpation and is sometimes associated with an abnormally increased skin thickness at birth. MR is a helpful noninvasive tool that may be used in infants for the detection of the enlarged tortuous vessels and AV shunting. These findings are more clearly delineated later in life with conventional arteriography. Lesions slowly enlarge over years and may cause distortion of facial features, visual loss, and cerebral hemorrhage.¹⁰⁶

Cobb syndrome

Cobb syndrome (cutaneomeningospinal angiomas) is the association of a dermatomal skin vascular malformation (trunk and arm or leg), a fast-flow intramedullary spinal AVM, and a vertebral vascular anomaly in the same segment. This metamerismic angiomas is the truncal counterpart of the syndromic cephalic AVMs. In infancy, this syndrome may be undiagnosed because the cutaneous vascular signs are subtle or are diagnosed as skin capillary malformation. Patients may present with neurologic symptoms in childhood or later in life. Hyperpigmentation has also been described overlying the spinal AVM.^{107,108} The diagnosis is often established later, when an abnormal vertebra is incidentally imaged or if neurologic symptoms of spinal cord compression occur. The existing literature on Cobb syndrome in infants needs to be interpreted with caution, given that some case reports of Cobb syndrome in infants actually represent segmental infantile hemangiomas associated with intraspinal hemangiomas or tethered cord.

Hereditary hemorrhagic telangiectasia

Also known as Osler–Weber–Rendu syndrome, hereditary hemorrhagic telangiectasia (HHT), is an autosomal dominant disorder with various phenotypes corresponding to at least three distinct genotypes.¹⁰⁹ Genetic testing makes early diagnosis available to relatives in a given affected family. HHT is characterized by skin and mucosal telangiectasia, spontaneous epistaxis and a risk of arteriovenous malformations in lungs, brain, and liver.¹¹⁰ Telangiectasia of the skin, lips, and mouth are not visible during infancy and mucosal and visceral hemorrhages are typically uncommon during this period. However, it is important to note that there are reports of infants of parents with known HHT presenting with intracranial hemorrhage in the neonatal period.¹¹¹

Ataxia–telangiectasia

This is a rare autosomal recessive disease characterized by progressive cerebellar ataxia, telangiectasia, elevated α -fetoprotein levels, B- and T-cell immunodeficiency with sinopulmonary infections, cancer susceptibility (especially hematologic malignancies and breast cancer), sensitivity to ionizing radiation and radiomimetic drugs, and premature aging.¹¹² The onset of telangiectasia in the newborn period is rare, however ocular telangiectasia may be noted in children as young as 1 year of age. In a group of 48 patients, the median age of onset of gait abnormalities was 15 months, and 72 months for telangiectasias. The median age of diagnosis was 78 months, shortly after the appearance of telangiectasia in two-thirds of patients.¹¹³ The mutated gene (*ATM*) maps to 11q22–23, and more than 400 mutations have been documented in affected individuals.

SYNDROMES ASSOCIATED WITH LYMPHATIC MALFORMATIONS

Gorham syndrome

This sporadic syndrome of progressive bony destruction is associated with a lymphatic malformation. Involvement of the skin and subcutaneous tissue is variable. Soft tissue masses as well as purple plaques have been described in association with the destructive bony lesions.¹¹⁴ The cause of the extensive bone destruction is not clearly understood. Lesions usually become obvious in childhood and the course is variable with some patients experiencing a period of stabilization after a period of osteolysis and other with more aggressive proliferation. Visceral life-threatening lymphatic anomalies, including pleural effusions, and gastrointestinal tract involvement, may develop in association with the bone-destructive process. Management of this disorder is challenging and includes supportive care. Surgical management and radiation therapy have been described but have been of limited effectiveness. More recently, medical therapies including anti-angiogenic agents such as interferon- α , bevacizumab and sirolimus are under investigation.^{115–117}

Hennekam syndrome

Hennekam syndrome, also known as generalized lymphatic dysplasia, is a rare diffuse lymphatic anomaly that is typically characterized by lymphedema of the extremities, which may be progressive and asymmetric, intestinal lymphangiectasia resulting in protein-losing enteropathy, developmental delay and abnormal fascias. Involvement of the pleura, pericardium, kidney and thyroid is reported.^{118–120} Autosomal recessive inheritance is suspected and in some cases it has been linked to mutations in the *CCBE1* gene.¹²¹ The expansion of the phenotype raises the question of more than one gene defect.

Hereditary cholestasis with lymphedema (Aagaes syndrome)

Hereditary cholestasis with lymphedema is an autosomal recessive disease that occurs mostly in infants of Norwegian ancestry. Significant leg lymphedema due to lymph vessel hypoplasia that is congenital or develops later in life, requires lifelong treatment. Cholestasis and obstructive jaundice are present at birth and may improve in adulthood, but in childhood, they may be lethal. Children have severe bleeding if vitamin K supplementation is not provided. They also complain of itching, and have growth retardation.

SYNDROMES ASSOCIATED WITH EITHER COMBINED MALFORMATIONS OR OVERGROWTH

Klippel–Trenaunay syndrome

Klippel and Trenaunay described the association of a port-wine stain (CM), venous anomaly and limb overgrowth in 1900. Since the first description, it has become well recognized that this group of patients are part of a heterogeneous spectrum and not all patients described in the literature have the same features. Over the last few years, there has been an attempt to refine the classification of this disorder with some authors restricting the designation of true Klippel–Trenaunay syndrome (KTS) to individuals with a combined capillary lymphatic-venous malformation, while others divide KTS into simple and complex forms based upon the presence or absence of lymphatic

anomalies, significant venous anomalies and a geographic stain.^{122–124} Regardless of the classification, the heterogeneity of features in patients diagnosed with KTS highlights the importance of recognizing early clues that might predict more significant overgrowth and complications. It is important to note that limb capillary malformations may occur without significant venous anomalies or overgrowth and these patients have a good prognosis. However, in the newborn period, it might be difficult for a less experienced clinician to predict which infants are more likely to have a milder course, therefore it is essential to reassess neonates and infants periodically for signs of more extensive involvement. The presence at birth of a sharply demarcated geographic stain on the external lateral aspect of the affected extremity, mainly the thigh, is predictive of associated lymphatic anomalies and a poorer prognosis. If there is an associated lymphatic anomaly, small hemorrhagic ‘blebs’, which are actually lymphatic vesicles are often visible from birth or develop during early infancy (Fig. 22.15).¹²⁵ Bony hypertrophy can increase progressively, resulting in a limb length discrepancy. Some infants have a milder presentation and course, with a large PWS involving a limb, soft tissue hypertrophy, but minimal to absent venous or lymphatic venous disease. These patients often have proportionate limb growth and a less morbid course than more severe cases of KTS. Recently, some authors have distinguished these patients from those with ‘true’ KTS. However, it becomes particularly important to follow young infants with limb PWS because venous anomalies may not become apparent until later in childhood.

Parkes Weber syndrome

Parkes Weber syndrome (PKWS) is the association of vascular stain, limb overgrowth (length and girth), and a fast-flow vascular anomaly with multiple arteriovenous shunts (Fig. 22.16). It is important to differentiate this disorder from KTS, as the prognosis is different. In rare instances, PKWS is complicated at birth by high-output cardiac failure. In the neonatal period, noninvasive assessment of PKWS is best done using ultrasound/color Doppler and MR angiography. Arteriography is usually not performed in the neonatal period, unless endovascular arterial embolization of the AVFs is mandatory to reduce the arterial overload accountable for congestive heart failure. Thus, KTS is a slow-flow vascular anomaly, whereas PKWS is a fast-flow vascular anomaly, but both can result in hypertrophy of the affected limb. Parkes Weber syndrome may occur as a manifestation of CM-AVM syndrome, therefore it is essential that a complete family history be obtained from affected individuals and genetic testing for *RASA1* mutations is recommended.

Diagnosis. These diagnoses are usually made clinically, but vascular imaging techniques help delineate the vascular defects. The differential diagnosis of KTS, especially severe cases, includes Proteus syndrome, PTEN hamartoma syndrome, MCAP and CLOVES syndrome (see below). Doppler ultrasound evaluation is helpful. MRI and MRA are helpful in more severe cases. Arteriography, phlebography, or lymphography are rarely needed during infancy and childhood. Routine screening for Wilms tumor, as advised in infants with congenital hemihypertrophy, is not necessary for individuals with true/classic KTS,¹²⁶ with the exception of patients having true generalized hemihypertrophy and KTS, or features that would suggest another overgrowth syndrome.¹²⁷

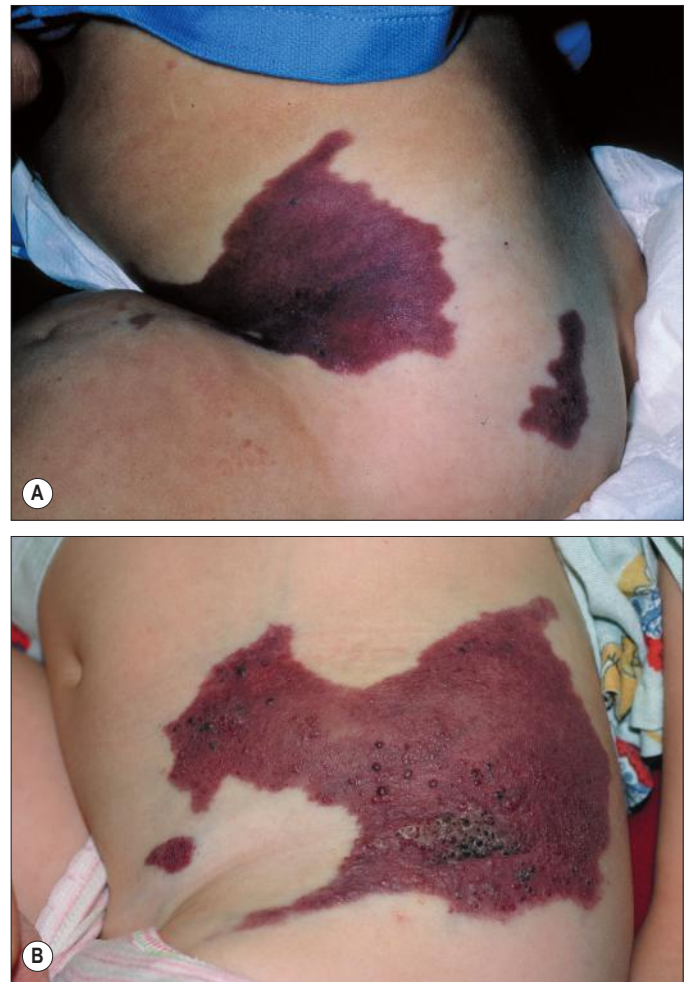


Figure 22.15 Klippel-Trenaunay syndrome with a prominent geographic stain on the abdomen, thigh, and buttock. Initially the stain is flat (A), but over time numerous ‘blebs’ develop on the surface due to increased lymphatic and venous pressure (B).



Figure 22.16 Parkes Weber syndrome in a newborn with evidence of a capillary lymphatic malformation, limb overgrowth, and arteriovenous fistulae (and cardiac failure) at birth.

Management. Therapeutic management includes close orthopedic follow-up of limb growth.¹²⁸ If limb length discrepancy is significant after 1 year of age, radiographic studies may be appropriate, and a shoe lift or other orthopedic appliance may be used. Ultimately, during infancy, if capillary stains are extensive, the use of a laser may be impractical, and responses on the extremities are poorer than at other sites.¹⁵ Varicosities worsen over time, and later in life, varicose veins develop in KTS. AV fistulae in PKWS in selected patients, may require treatment. Ideally, patients with slow-flow vascular anomalies of the limb should use compressive stockings, but proper fitting is difficult in infants and young children who are undergoing rapid somatic growth. Low-grade clotting and consumption coagulopathy similar to that seen in venous malformations can be seen in KTS (see above). Deep vein thrombosis is rare and pulmonary embolism is an infrequent but life-threatening event.¹²⁹ Long-term iatrogenic complications and a bad cosmetic outcome can result from overenthusiastic aggressive treatments early in life. Parents need educational information and support, both in the newborn period and over time. A multidisciplinary approach is important, especially in the more severe cases.

CLOVES syndrome

CLOVES syndrome refers to congenital lipomatous overgrowth, vascular malformations, epidermal nevi and skeletal anomalies/scoliosis. It is a newly described overgrowth syndrome resulting from post-zygotic activation mutations in the PIK3CA gene.¹³⁰ In CLOVES, the large lipomatous masses are usually present on the trunk and lead to scoliosis of the spine. Other skeletal anomalies include macrodactyly and a widened space between the first and second toes, known as a sandal-gap deformity. Most patients with CLOVES syndrome have vascular malformations, most commonly CM or CLVM, however fast-flow lesions (spinal AVMs) are also described.¹³¹ In the past, patients with CLOVES were often misdiagnosed as having KT or Proteus syndrome, as there is considerable clinical overlap (Fig. 22.17). The identification of similar gene mutations in CLOVES, Proteus and MCAP (see above) suggests a common lineage, where each syndrome results from a mutation within the same molecular pathway (Fig. 22.18). Like many of the complex overgrowth syndromes, screening for Wilms tumor is also recommended.

Proteus syndrome

Proteus syndrome, first described by Wiedemann and colleagues,¹³² is characterized by asymmetric localized overgrowth of various body parts, affecting soft tissues and bones. It is caused by mutations in the AKT1 gene.¹³³ The syndrome may be evident at birth, but a progressive course and mosaic distribution of the lesions are characteristic and necessary for diagnosis.^{134,135} The most characteristic features are the asymmetric, disproportionate growth with regional gigantism and cutaneous manifestations, including connective tissue nevus (cerebri-form dermal thickening of soles and palms), epidermal nevi, lipomas, café-au-lait spots, and vascular malformations of the slow-flow type, such as extensive CLVMs.^{134,135} Visceral benign tumors, mainly lipomas, but tumors in the endocrine glands or CNS, and visceral vascular malformations are also observed. Intelligence is normal in most patients, but learning disabilities are present in one-third. Ophthalmologic and neurologic alterations or seizures have been reported. Surgical reconstruction is the primary treatment for these children. A multidisciplinary



Figure 22.17 (A) A 19-month-old baby with CLOVES syndrome. Note the asymmetric lipomatous overgrowth and capillary malformations. (B) Appearance of CLOVES later in childhood with truncal lipomatosis and scoliosis in a different patient.

approach, including orthopedic management is essential because of discrepancies in limb and foot growth. Excision of lipomas or laser treatment of vascular lesions is sometimes indicated. The differential diagnosis for Proteus syndrome includes KTS, CLOVES, SOLAMEN and MCM/MCAP. Recent advances have led to the discovery of the specific genetic mutations of each of these conditions, where affected genes are involved in the same molecular signaling pathway (AKT1/PIK3CA). AKT1 is activated by loss of function mutations in PTEN, which helps to explain why patients with PTEN mutations (SOLAMEN, Cowden) have some overlapping yet distinct features (Table 22.3, Fig. 22.18).

PTEN hamartoma tumor syndrome

The PTEN gene encodes for a tumor suppressor phosphatase that has been implicated in familial cancer syndromes. The PTEN hamartoma tumor syndrome is the name given recently to this group of familial syndromes, which includes Cowden and Bannayan–Riley–Ruvalcaba syndromes (BRRS). Cowden syndrome is associated with a high risk for the development

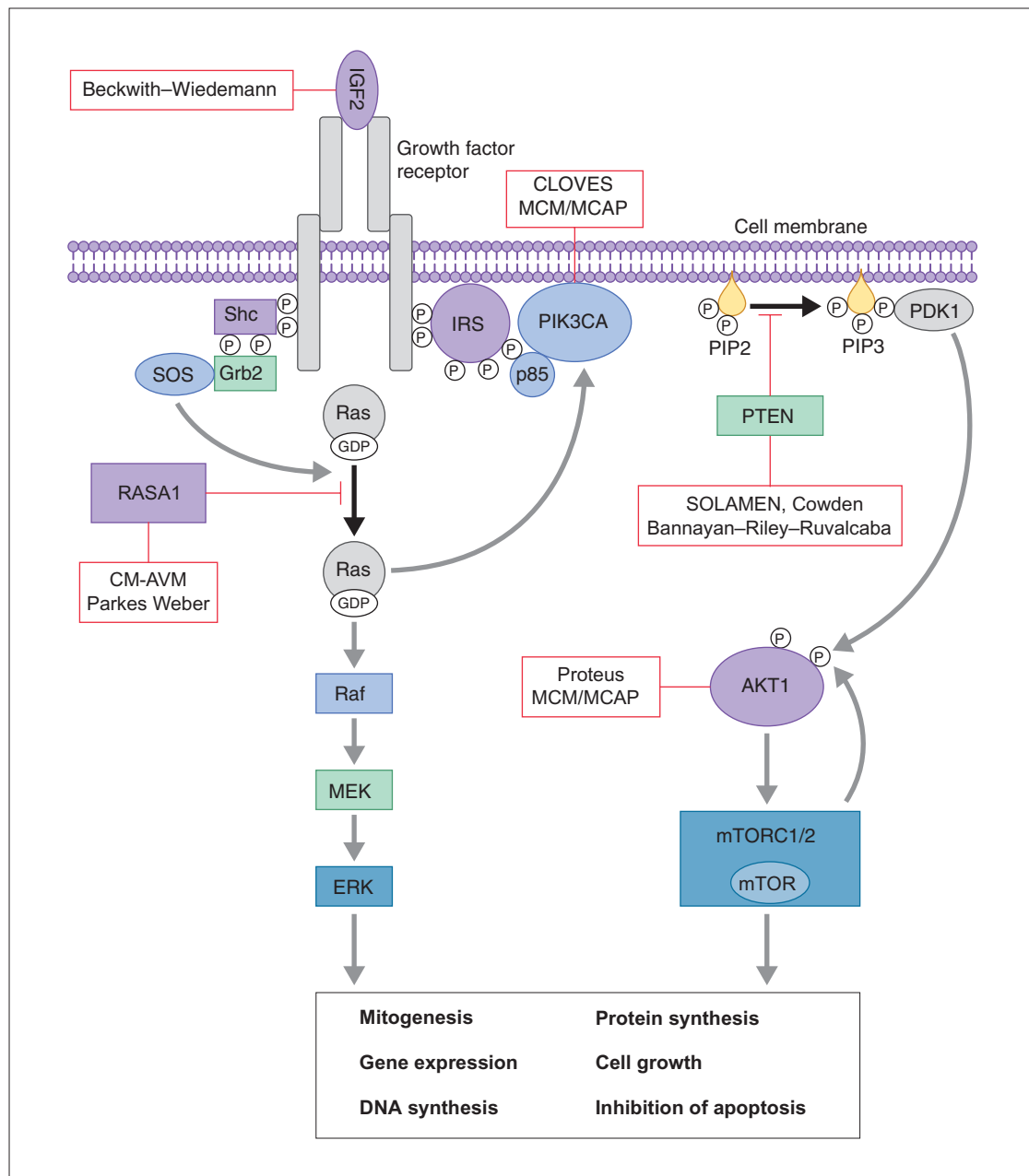


Figure 22.18 PIK3CA/AKT1 molecular pathway. Mutations within key proteins in the Ras/Raf/MEK/ERK and Ras/PIK3CA/PTEN/AKT1/mTOR pathways have been identified in a number of vascular malformation and overgrowth syndromes. In Beckwith–Wiedemann syndrome, genomic imprinting errors result in biallelic overexpression of the growth factor IGF2. RASA1 mutations occur in CM-AVM syndrome and Parkes Weber syndrome. CLOVES and MCM/MCAP are associated with mutations in PIK3CA. PTEN mutations have been identified in patients with SOLAMEN and the PTEN hamartoma tumor syndromes including Cowden’s and Bannayan–Riley–Ruvalcaba. Finally, AKT1 mutations have been implicated in Proteus and some forms of MCM/MCAP. (Courtesy of William Tsiaras, MD, PhD.)

of cutaneous hamartomas and internal malignancies such as breast, thyroid and endometrial carcinoma. BRRS is an autosomal dominant disorder characterized by macrocephaly, developmental delay and penile lentigines. Both syndromes are due to mutations in the PTEN gene, which suggests a similar risk for the development of malignancy.¹³⁶ In both syndromes, associated vascular malformations are frequently described and usually consist of high flow, intramuscular vascular anomalies associated with increased adipose tissue. These vascular malfor-

mations have been found to be quite specific to PTEN hamartoma tumor syndromes and should prompt investigation, workup and continued monitoring for early-onset malignancies in suspected cases.¹³⁷ See Chapter 29 for further discussion on selected genetic overgrowth syndromes.



KEY REFERENCES

1. Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg* 1982;69:412–20.
6. Juern AM, Glick ZR, Drolet BA, et al. Nevus simplex: a reconsideration of nomenclature, sites of involvement, and disease associations. *J Am Acad Dermatol* 2010;63(5):805–14.
9. Frelin LP, Cohen B, North PE, et al. Sturge–Weber syndrome and port-wine stains caused by somatic mutation in *GNAQ*. *N Engl J Med* 2013;368:1971–9.
19. Huikeshoven M, Koster PH, de Borgie CA, et al. Redarkening of port-wine stains 10 years after laser treatment. *N Engl J Med* 2007;356(12):1235–40.
37. Limaye N, Wouters V, Uebelhoer M, et al. Somatic mutations in angiopoietin receptor gene *TEK* cause solitary and multiple sporadic venous malformations. *Nat Genet* 2009;41(1):118–24.
42. Domp Martin A, Acher A, Thibon P, et al. Association of localized intravascular coagulopathy with venous malformations. *Arch Dermatol* 2008;144(7):873–7.
72. Lo W, Marchuk DA, Ball KL, et al; Brain Vascular Malformation Consortium National Sturge–Weber Syndrome Workgroup. Updates and future horizons on the understanding, diagnosis, and treatment of Sturge–Weber syndrome brain involvement. *Dev Med Child Neurol* 2012;54:214–23. Erratum in: *Dev Med Child Neurol* 2012;54(10):957.
90. Kienast AK, Hoeger PH. Cutis marmorata telangiectatica congenita: a prospective study of 27 cases and review of the literature with proposal of diagnostic criteria. *Clin Exp Dermatol* 2009;34:319–23.
125. Maari C, Frieden IJ. Klippel–Trenaunay syndrome: the importance of ‘geographic stains’ in identifying lymphatic disease and risk of complications. *J Am Acad Dermatol* 2004;51:391–8.
133. Lindhurst MJ, Sapp JC, Teer JK, et al. A mosaic activating mutation in *AKT1* associated with the Proteus syndrome. *N Engl J Med* 2011;365(7):611–19.

REFERENCES

- Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. *Plast Reconstr Surg* 1982;69:412–20.
- Enjolras O, Mulliken J. Vascular tumors and vascular malformations, new issues. *Adv Dermatol* 1998;13:375–423.
- Takahashi K, Mulliken JB, Kozakewich H, et al. Cellular markers that distinguish the phases of hemangioma during infancy and childhood. *J Clin Invest* 1994;93:2357–64.
- Requena L, Sanguenza OP. Cutaneous vascular proliferations. II. Hyperplasias and benign neoplasms. *J Am Acad Dermatol* 1997;37:887–920.
- Leung AK, Telmesani AM. Salmon patches in Caucasian children. *Pediatr Dermatol* 1989;6:185–7.
- Juerm AM, Glick ZR, Drolet BA, et al. Nevus simplex: a reconsideration of nomenclature, sites of involvement, and disease associations. *J Am Acad Dermatol* 2010;63(5):805–14.
- Maniscalco M, Guareschi E, Noto G, et al. Midline telangiectatic nevus (salmon patch) of the nape of the neck. *Eur J Pediatr Dermatol* 2003;13:81–4.
- Jacobs AH, Cahn RL. Birthmarks. *Pediatr Ann* 1976;5(12):743–58.
- Frelin LP, Cohen B, North PE, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in *GNAQ*. *N Engl J Med* 2013;368:1971–9.
- Cordoro KM, Speetzen LS, Koerper MA, et al. Physiologic changes in vascular birthmarks during early infancy: Mechanisms and clinical implications. *J Am Acad Dermatol* 2009;60(4):669–75.
- McClean K, Hanke CW. The medical necessity for treatment of port-wine stains. *Dermatol Surg* 1997;23:663–7.
- Boyd JB, Mulliken JB, Kaban LB, et al. Skeletal changes associated with vascular malformations. *Plast Reconstr Surg* 1984;74:789–95.
- Lanigan SW, Taibjee SM. Recent advances in laser treatment of port-wine stains. *Br J Dermatol* 2004;151:527–33.
- Renfro L, Geronemus RG. Anatomical differences of port-wine stains in response to treatment with the pulsed dye laser. *Arch Dermatol* 1993;129:182–8.
- Sommer S, Seukeran DC, Sheehan-Dare RA. Efficacy of pulsed dye laser treatment of port-wine stain malformations of the lower limb. *Br J Dermatol* 2003;149:770–5.
- Ashinoff R, Geronemus RG. Flashlamp-pumped pulsed dye laser for port-wine stains in infancy: earlier versus later treatment. *J Am Acad Dermatol* 1991;24:467–72.
- Van Der Horst C, Koster P, De Borgie C, et al. Effect of the timing on the treatment of port-wine stains with the flash-lamp-pumped pulsed-dye laser. *N Engl J Med* 1998;338:1028–33.
- Chapas AM, Eickhorst K, Geronemus RG. Efficacy of early treatment of facial port-wine stains in newborns: a review of 49 cases. *Lasers Surg Med* 2007;39(7):563–8.
- Huikeshoven M, Koster PH, de Borgie CA, et al. Redarkening of port-wine stains 10 years after laser treatment. *N Engl J Med* 2007;356(12):1235–40.
- Yang MU, Yaroslavsky AN, Farinelli WA, et al. Longpulsed neodymium:yttrium-aluminum-garnet laser treatment for port-wine stains. *J Am Acad Dermatol* 2005;52(3 Pt 1):480–90.
- Kono T, Frederick Groff W, Chan HH, et al. Longpulsed neodymium:yttrium-aluminum-garnet laser treatment for hypertrophic port-wine stains on the lips. *J Cosmet Laser Ther* 2009;11(1):11e3.
- Borges da Costa J, Boixeda P, Moreno C, et al. Treatment of resistant port-wine stains with a pulsed dual wavelength 595 and 1064 nm laser: a histochemical evaluation of the vessel wall destruction and selectivity. *Photomed Laser Surg* 2009;27(4):599–605.
- Alster TS, Tanzi EL. Combined 595-nm and 1,064-nm laser irradiation of recalcitrant and hypertrophic portwine stains in children and adults. *Dermatol Surg* 2009;35(6):914–18.
- Izikson L, Nelson JS, Anderson RR. Treatment of hypertrophic and resistant port-wine stains with a 755 nm laser: a case series of 20 patients. *Lasers Surg Med* 2009;41(6):427–32.
- Ho WS, Ying SY, Chan PC, et al. Treatment of port-wine stains with intense pulsed light: a prospective study. *Dermatol Surg* 2004;30(6):887–90.
- Reynolds N, Exley J, Hills S, et al. The role of the Lumina intense pulsed light system in the treatment of port-wine stains: a case controlled study. *Br J Plast Surg* 2005;58(7):968–80.
- Raulin C, Schroeter CA, Weiss RA, et al. Treatment of port-wine stains with a noncoherent pulsed light source: a retrospective study. *Arch Dermatol* 1999;135(6):679–83.
- Ozdemir M, Engin B, Mevlitoglu I. Treatment of facial port-wine stains with intense pulsed light: a prospective study. *J Cosmet Dermatol* 2008;7(2):127–31.
- Bjerring P, Christiansen K, Troilius A. Intense pulsed light source for the treatment of dye laser resistant port-wine stains. *J Cosmet Laser Ther* 2003;5(1):7–13.
- Faurschou A, Togsverd-Bo K, Zachariae C, et al. Pulsed dye laser vs. intense pulsed light for portwine stains: a randomized side-by-side trial with blinded response evaluation. *Br J Dermatol* 2009;160(2):359–64.
- Yuan K, Li Q, Yu W, et al. Comparison of photodynamic therapy and pulsed dye laser in patients with port-wine stain birthmarks: a retrospective analysis. *Photodiagnosis Photodyn Ther* 2008;5(1):50–7.
- Yuan K, Li Q, Yu W, et al. Photodynamic therapy in treatment of port-wine stain birthmarks, recent progress. *Photodiagnosis Photodyn Ther* 2009;6(3–4):189–94.
- Gu Y, Huang NY, Liang J, et al. Clinical study of 1949 cases of port-wine stains treated with vascular photodynamic therapy (Gu's PDT). *Ann Dermatol Venereol* 2007;134.
- Evans AV, Robson A, Barlow RJ, et al. Treatment of port-wine stains with photodynamic therapy, using pulsed dye laser as a light source, compared with pulsed dye laser alone: a pilot study. *Lasers Surg Med* 2005;36(4):266–9.
- Chang C, Hsiao Y, Mihm MC, et al. Pilot study examining the combined use of pulsed dye laser and topical Imiquimod versus laser alone for treatment of port-wine stain birthmarks. *Lasers Surg Med* 2008;40(9):605–10.
- Vikkula M, Boon LM, Carraway KL, et al. Vascular dysmorphogenesis caused by an activating mutation in the receptor tyrosine kinase TIE2. *Cell* 1996;87:1181–90.
- Limaye N, Wouters V, Uebelhoer M, et al. Somatic mutations in angiopoietin receptor gene TEK cause solitary and multiple sporadic venous malformations. *Nat Genet* 2009;41(1):118–24.
- Boon LM, Mulliken JB, Enjolras O, et al. Glomovenous malformation (glomangioma) and venous malformation. *Arch Dermatol* 2004;140:971–6.
- Brouillard P, Ghassibe M, Penington A, et al. Four common glomulin mutations cause two thirds of glomovenous malformations ('familial glomangiomas'): evidence for a founder effect. *J Med Genet* 2005;42:e13.
- Enjolras O, Ciabrini D, Mazoyer E, et al. Extensive pure venous malformations in the upper and lower limbs: a review of 27 cases. *J Am Acad Dermatol* 1997;36:219–25.
- Mazoyer E, Enjolras O, Laurian C, et al. Coagulation abnormalities associated with extensive venous malformations of the limbs: differentiation from Kasabach-Merritt syndrome. *Clin Lab Haematol* 2002;24:243–51.
- Domp Martin A, Acher A, Thibon P, et al. Association of localized intravascular coagulopathy with venous malformations. *Arch Dermatol* 2008;144(7):873–7.
- Burrows PE, Mason KP. Percutaneous treatment of low flow vascular malformations. *J Vasc Interv Radiol* 2004;15:431–45.
- Domp Martin A, Ballieux F, Thibon P, et al. Elevated D-dimer level in the differential diagnosis of venous malformations. *Arch Dermatol* 2009;145(11):1239–44.
- Puig S, Aref H, Chigot V, et al. Classification of venous malformations in children and implications for sclerotherapy. *Pediatr Radiol* 2003;33(2):99–103.
- Boukobza M, Enjolras O, Guichard JP, et al. Cerebral developmental venous anomaly associated with head and neck venous malformations. *Am J NeuroRadiol* 1996;17:987–94.
- Mathes EF, Haggstrom AN, Dowd C, et al. Clinical characteristics and management of vascular anomalies: findings of a multidisciplinary vascular anomalies clinic. *Arch Dermatol* 2004;140(8):979–83.
- Kok K, McCafferty I, Monaghan A, et al. Percutaneous sclerotherapy of vascular malformations in children using sodium tetradecyl sulphate: The Birmingham experience. *J Plast Reconstr Aesthet Surg* 2012;65(11):1451–60.
- Barranco-Pons R, Burrows PE, Landrigan-Ossar M, et al. Gross hemoglobinuria and oliguria are common transient complications of sclerotherapy for venous malformations: review of 475 procedures. *AJR Am J Roentgenol* 2012;199(3):691–4.
- Gelbert F, Enjolras O, Deffrenne D, et al. Percutaneous sclerotherapy for venous malformation of the lips: a retrospective study in 23 patients. *Neuroradiology* 2000;42:692–6.
- Fayad L, Hazirolan T, Bluemke D, et al. Vascular malformations in the extremities: emphasis of MR imaging features that guide treatment options. *Skeletal Radiol* 2006;35:127–37.
- Mazoyer E, Enjolras O, Bisdorff A, et al. Coagulation disorders in patients with venous malformation of the limbs and trunk: a case series of 118 patients. *Arch Dermatol* 2008;144(7):861–7.

53. Adams DM. Special considerations in vascular anomalies: hematologic management. *Clin Plast Surg* 2011;38(1):153–60.
54. Brouillard P, Vikkula M. Genetic causes of vascular malformations. *Hum Mol Genet* 2007;1140–9.
55. Limaye N, Boon LM, Vikkula M. From germline towards somatic mutations in the pathophysiology of vascular anomalies. *Hum Mol Genet* 2009;18(R1):R65–74.
56. Tanriverdi HA, Hendrick HJ, Ertan AK, et al. Hygroma colli cysticum: prenatal diagnosis and prognosis. *Am J Perinatol* 2001;18:415–20.
57. Davies D, Rogers M. Morphology of lymphatic malformations: a pictorial review. *Aust J Dermatol* 2000;41:1–7.
58. Padwa BL, Hayward PG, Ferrero NF, et al. Cervicofacial lymphatic malformation, clinical course, surgical intervention, and pathogenesis of skeletal hypertrophy. *Plast Reconstr Surg* 1995;95:951–60.
59. Edwards PD, Rahbar R, Ferraro NF, et al. Lymphatic malformation of the lingual base and oral floor. *Plast Reconstr Surg* 2005;115:1906–15.
60. Greene AK, Burrows PE, Smith L, et al. Periorbital lymphatic malformation: clinical course and management in 42 patients. *Plast Reconstr Surg* 2005;115:22–30.
61. Orvidas LJ, Kasperbauer JL. Pediatric lymphangiomas of the head and neck. *Ann Otol Rhinol Laryngol* 2000;109:411–21.
62. Hayward PG, Orgill DP, Mulliken JB, et al. Congenital fibrosarcoma masquerading as lymphatic malformation: report of two cases. *J Pediatr Surg* 1995;30:84–8.
63. Enjolras O, Deffrennes D, Borsik M, et al. Les 'tumeurs' vasculaires. Règles de prise en charge chirurgicale. *Ann Chir Plast Esthet* 1998;43:455–90.
64. Luzzato C, Midrio P, Tchaprassian Z, et al. Sclerosing treatment of lymphangiomas with OK-432. *Arch Dis Child* 2000;82:316–18.
65. Kim SW, Kavanagh K, Orbach DB, et al. Long-term outcome of radiofrequency ablation for intraoral microcystic lymphatic malformation. *Arch Otolaryngol Head Neck Surg* 2011;137(12):1247–50.
66. Grimmer JF, Mulliken JB, Burrows PE, et al. Radiofrequency ablation of microcystic lymphatic malformation in the oral cavity. *Arch Otolaryngol Head Neck Surg* 2006;132(11):1251–6.
67. Huang JT, Liang MG. Vascular malformations. *Pediatr Clin North Am* 2010;57(5):1091–110.
68. Kohout MP, Hansen M, Pribaz JJ, et al. Arteriovenous malformations of the head and neck: natural history and management. *Plast Reconstr Surg* 1998;102(3):643–54.
69. Wu JK, Bisdorff A, Gelbert F, et al. Auricular arteriovenous malformation: evaluation, management, and outcome. *Plast Reconstr Surg* 2005;115(4):985–95.
70. Greene AK, Orbach DB. Management of arteriovenous malformations. *Clin Plast Surg* 2011;38(1):95–106.
71. Enjolras O, Riché MC, Merland JJ. Facial portwine stains and Sturge–Weber syndrome. *Pediatrics* 1985;76:48–51.
72. Lo W, Marchuk DA, Ball KL, et al. Brain Vascular Malformation Consortium National Sturge–Weber Syndrome Workgroup. Updates and future horizons on the understanding, diagnosis, and treatment of Sturge–Weber syndrome brain involvement. *Dev Med Child Neurol* 2012;54:214–23. Erratum in: *Dev Med Child Neurol* 2012;54(10):957.
73. Adamsbaum C, Pinton F, Rolland Y, et al. Accelerated myelination in early Sturge–Weber syndrome: MRI–SPECT correlation. *Pediatr Radiol* 1996;26:759–62.
74. Pinton F, Chiron C, Enjolras O, et al. Early single photon emission computed tomography in Sturge–Weber syndrome. *J Neurol Neurosurg Psychiatry* 1997;63:616–21.
75. Chugani HT. The role of PET in childhood epilepsy. *J Child Neurol* 1994;9:82–8.
76. Ville D, Enjolras O, Chiron C, et al. Prophylactic antiepileptic treatment in Sturge–Weber disease. *Seizure* 2002;11:145–50.
77. Lance EI, Sreenivasan AK, Zabel TA, et al. Aspirin use in Sturge–Weber syndrome: side effects and clinical outcomes. *J Child Neurol* 2013;28(2):213–18.
78. Wright DR, Frieden IJ, Orlow SJ, et al. The misnomer 'macrocephaly-cutis marmorata telangiectatica congenita syndrome': report of 12 new cases and support for revising the name to macrocephaly-capillary malformations. *Arch Dermatol* 2009;145(3):287–93.
79. Toriello HV, Mulliken JB. Accurately renaming macrocephaly-cutis marmorata telangiectatica congenita (M-CMTC) as macrocephaly-capillary malformation (M-CM). *Am J Med Genet A* 2007;143A(24):3009.
80. Rivière JB, Mirzaa GM, O'Roak BJ, et al. De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. *Nat Genet* 2012;44(8):934–40.
81. Poole RL, Leith DJ, Docherty LE, et al. Beckwith–Wiedemann syndrome caused by maternally inherited mutation of an OCT-binding motif in the IGF2/H19-imprinting control region, ICR1. *Eur J Hum Genet* 2012;20(2):240–3.
82. Happle R. Phacomatosis pigmentovascularis revisited and reclassified. *Arch Dermatol* 2005;141(3):385–8.
83. Fernández-Guarino M, Boixeda P, de Las Heras E, et al. Phacomatosis pigmentovascularis: Clinical findings in 15 patients and review of the literature. *J Am Acad Dermatol* 2008;58(1):88–93.
84. Boon LM, Ballieux F, Vikkula M. Pathogenesis of vascular anomalies. *Clin Plast Surg* 2011;38(1):7–19.
85. Nahm WK, Moise S, Eichenfield LF, et al. Venous malformations in blue rubber bleb nevus syndrome: variable onset of presentation. *J Am Acad Dermatol* 2004;50(Suppl. 5):S101–6.
86. Fishman SJ, Smithers CJ, Folkman J, et al. Blue rubber bleb nevus syndrome: surgical eradication of gastrointestinal bleeding. *Ann Surg* 2005;241(3):523–8.
87. Pansuriya TC, Kroon HM, Bovée JV. Enchondromatosis: insights on the different subtypes. *Int J Clin Exp Pathol* 2010;3(6):557–69.
88. Pansuriya TC, van Eijk R, d'Adamo P, et al. Somatic mosaic IDH1 and IDH2 mutations are associated with enchondroma and spindle cell hemangioma in Ollier disease and Maffucci syndrome. *Nat Genet* 2011;43(12):1256–61.
89. Picascia DD, Esterly NB. Cutis marmorata telangiectatica congenita: report of 22 cases. *J Am Acad Dermatol* 1989;20:1098–104.
90. Kienast AK, Hoeger PH. Cutis marmorata telangiectatica congenita: a prospective study of 27 cases and review of the literature with proposal of diagnostic criteria. *Clin Exp Dermatol* 2009;34:319–23.
91. Enjolras O. Cutis marmorata telangiectatica congenita. *Ann Dermatol Venerol* 2001;128:161–6.
92. Dyall-Smith D, Ramsden A, Laurie S. Adams–Oliver syndrome: aplasia cutis congenita, terminal transverse limb defects, and cutis marmorata telangiectatica congenita. *Australas J Dermatol* 1994;35:19–22.
93. Moroz PK. Cutis marmorata telangiectatica congenita: long-term follow-up, review of the literature, and report of a case in conjunction with congenital hypothyroidism. *Pediatr Dermatol* 1993;10:6–11.
94. Devillers ACA, de Waard-Van der Spek FB, Oranje AP. Cutis marmorata telangiectatica congenita: clinical features in 35 cases. *Arch Dermatol* 1999;135:34–8.
95. Gelmetti C, Schianchi R, Ermacora E. Cutis marmorata telangiectatica congenita: quatre nouveaux cas et revue de la littérature. *Ann Dermatol Venerol* 1987;114:1517–28.
96. Fujita M, Darmstadt GL, Dinulos JG. Cutis marmorata telangiectatica congenita with hemangiomatous histopathologic features. *J Am Acad Dermatol* 2003;48:950–4.
97. Carrascosa JM, Ribera M, Bielsa I, et al. Cutis marmorata telangiectatica congenita or neonatal lupus? *Pediatr Dermatol* 1996;13:230–2.
98. Imperial R, Helwig EB. Verrucous hemangioma. A clinicopathologic study of 21 cases. *Arch Dermatol* 1967;96:247–53.
99. Tennant LB, Mulliken JB, Perez-Atayde AR, et al. Verrucous hemangioma revisited. *Pediatr Dermatol* 2006;23:208–15.
100. Rossi A, Bozzi M, Barra E. Verrucous hemangioma and angiokeratoma circumscriptum: clinical and histologic differential characteristics. *J Dermatol Surg Oncol* 1989;15:88–91.
101. Popadić M. Dermoscopic diagnosis of a rare, congenital vascular tumor: Verrucous hemangioma. *J Dermatol* 2012;39(12):1049–50.
102. Clairwood MQ, Bruckner AL, Dadras SS. Verrucous hemangioma: a report of two cases and review of the literature. *J Cutan Pathol* 2011;38:740–6.
103. Al Dhaybi R, Powell J, McCuaig C, et al. Differentiation of vascular tumors from vascular malformations by expression of Wilms tumor 1 gene: evaluation of 126 cases. *J Am Acad Dermatol* 2010;63:1052–7.
104. Eerola I, Boon LM, Mulliken JB, et al. Capillary malformation arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. *Am J Hum Genet* 2003;73:1240–9.
105. Chee D, Phillips R, Maixner W, et al. The potential of capillary birthmarks as a significant marker for capillary malformation-arteriovenous malformation syndrome in children who had nontraumatic cerebral hemorrhage. *J Pediatr Surg* 2010;45(12):2419–22.
106. Dayani PN, Sadun AA. A case report of Wyburn–Mason syndrome and review of the literature. *Neuroradiology* 2007;49:445–56.
107. Clark MT, Brooks EL, Chong W, et al. Cobb syndrome: a case report and systematic review of the literature. *Pediatr Neurol* 2008;39:423–5.
108. Spiotta AM, Hussain MS, Masaryk TJ, et al. Combined endovascular and surgical resection of a giant lumbosacral arteriovenous malformation in a patient with Cobb syndrome. *J Neurointerv Surg* 2011;3:293–6.

109. Whitehead KJ, Smith MC, Li DY. Arteriovenous malformations and other vascular malformation syndromes. *Cold Spring Harb Perspect Med* 2012;3(2):a006635.
110. Begbie ME, Wallace GM, Shovlin CL. Hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): a view from the 21st century. *Postgrad Med J* 2003;79:18–24.
111. Delaney HM, Rooks VJ, Wolfe SQ, et al. Term neonate with intracranial hemorrhage and hereditary hemorrhagic telangiectasia: a case report and review of the literature. *J Perinatol* 2012;32:642–4.
112. Verhagen MM, Last JJ, Hogervorst FB, et al. Presence of ATM protein and residual kinase activity correlates with the phenotype in ataxia-telangiectasia: a genotype-phenotype study. *Hum Mutat* 2012;33(3):561–71.
113. Cabana M, Crawford TO, Winkelstein JA, et al. Consequences of the delayed diagnosis of ataxia-telangiectasia. *Pediatrics* 1998;102:98–100.
114. Leite I, Hernandez-Martin A, Colmenero I, et al. Invasive lymphatic malformation (Gorham-Stout) of the pelvis with prominent skin involvement. *Pediatr Dermatol* 2013; 30(3):374–8.
115. Hammer F, Kenn W, Wesselmann U, et al. Gorham-Stout disease – stabilization during bisphosphonate treatment. *J Bone Miner Res* 2005;20:350–3.
116. Grunewald TG, Damke L, Maschan M, et al. First report of effective and feasible treatment of multifocal lymphangiomatosis (Gorham-Stout) with bevacizumab in a child. *Ann Oncol* 2010;21:1733–4.
117. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer* 2011;57:1018–24.
118. Hennekam RC, Geerdink RA, Hamel BC, et al. *Am J Med Genet* 1989;34:593–600.
119. Van Balkom ID, Alders M, Allanson J, et al. Lymphedema-lymphangiectasia-mental retardation (Hennekam) syndrome: a review. *Am J Med Genet* 2002;112:412–21.
120. Musumeci ML, Nasca MR, De Pasquale R, et al. Cutaneous manifestations and massive genital involvement in Hennekam syndrome. *Pediatr Dermatol* 2006;23:239–42.
121. Connell FC, Gordon K, Brice G, et al. The classification and diagnostic algorithm for primary lymphatic dysplasia: an update from 2010 to include molecular findings. *Clin Genet* 2013; 84(4):303–14.
122. Oduer CE, van der Horst CM, Hennekam RC. Klippel-Trenaunay syndrome: diagnostic criteria and hypothesis on etiology. *Ann Plast Surg* 2008;60(2):217–23.
123. Schook CC, Mulliken JB, Fishman SJ, et al. Differential diagnosis of lower extremity enlargement in pediatric patients referred with a diagnosis of lymphedema. *Plast Reconstr Surg* 2011;127(4):1571–81.
124. Redondo P, Aguado L, Martínez-Cuesta A. Diagnosis and management of extensive vascular malformations of the lower limb: part I. Clinical diagnosis. *J Am Acad Dermatol* 2011;65(5):893–906; quiz 907–8.
125. Maari C, Frieden IJ. Klippel-Trenaunay syndrome: the importance of ‘geographic stains’ in identifying lymphatic disease and risk of complications. *J Am Acad Dermatol* 2004;51: 391–8.
126. Greene AK, Kieran M, Burrows PE, et al. Wilms’ tumor screening is unnecessary in Klippel-Trenaunay syndrome. *Pediatrics* 2004; 113:e326–9.
127. Kundu RV, Frieden IJ. Presence of vascular anomalies with congenital hemihypertrophy and Wilms’ tumor: an evidence-based evaluation. *Pediatr Dermatol* 2003;20:199–206.
128. Enjolras O, Chapot R, Merland JJ. Vascular anomalies and the growth of limbs. *J Pediatr Orthop B* 2004;13:349–57.
129. Huiras EE, Barnes CJ, Eichenfield LF, et al. Pulmonary thromboembolism associated with Klippel-Trenaunay syndrome. *Pediatrics* 2005; 116:e596–600.
130. Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. *Am J Hum Genet* 2012; 90(6):1108–15.
131. Alomari AI, Chaudry G, Rodesch G, et al. Complex spinal-paraspinal fast-flow lesions in CLOVES syndrome: analysis of clinical and imaging findings in 6 patients. *Am J Neuroradiol* 2011;32(10):1812–17.
132. Wiedemann HR, Burgio GR, Aldendorff P, et al. The Proteus syndrome. *Eur J Pediatr* 1983;140:5–12.
133. Lindhurst MJ, Sapp JC, Teer JK, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. *N Engl J Med* 2011; 365(7):611–19.
134. Hoeger PH, Martinez A, Maerker J, et al. Vascular anomalies in Proteus syndrome. *Clin Exp Dermatol* 2004;29:222–30.
135. Nguyen D, Turner JT, Olsen C, et al. Cutaneous manifestations of Proteus syndrome. *Arch Dermatol* 2004;140:947–53.
136. Eng C. PTEN: one gene, many syndromes. *Hum Mutat* 2003;22(3):183–98.
137. Kurek KC, Howard E, Tennant LB, et al. PTEN hamartoma of soft tissue: a distinctive lesion in PTEN syndromes. *Am J Surg Pathol* 2012; 36(5):671–87.

Hypopigmentation Disorders

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Introduction

A diverse group of conditions present with hypopigmentation in neonates and infants. A practical clinical approach would be to categorize them according to the distribution of the hypopigmentation: generalized, mosaic, or localized (Box 23.1). Some may be present at birth, but not noticed until later in infancy because neonates often have a lighter skin at birth than in later life.

Any defect occurring in melanocyte development, melanin synthesis and transport, or distribution of melanosomes to keratinocytes can result in a hypopigmentary disorder. Melanocytes originate from the neural crest and are located in the epidermis, hair bulb, eye (choroid, ciliary body, iris), inner ear (cochlea) and central nervous system (leptomeninges). Melanin is synthesized in melanosomes, which are organelles that share characteristics with lysosomes.

This chapter discusses a variety of clinical conditions causing hypopigmentation in neonates and infants, many of which have a genetic basis.

Generalized hypopigmentation of skin, hair, and eyes

OCULOCUTANEOUS ALBINISM

Oculocutaneous albinism (OCA) refers to a group of autosomal recessive disorders involving abnormal melanin synthesis. Affected individuals have absent (type 1A) or reduced (type 1B, 2, 3, and 4) pigmentation in the skin, hair, and eyes from birth. The color varies from white to light brown, depending on ethnicity and the specific type of OCA. Ocular manifestations include nystagmus, photophobia, and decreased visual acuity. These are caused by decreased melanin within the eye or misrouting of optic nerve fibers. The affected infant is typically less pigmented than unaffected siblings.

Historically, OCA was divided into two clinical types based on the presence or absence of tyrosinase, the rate-limiting enzyme in the melanin biosynthetic pathway.¹ Advances in molecular genetics have given rise to a more accurate classification and better understanding of pathogenesis.^{2,3} In OCA, epidermal and follicular melanocytes are present in normal quantity and distribution but do not synthesize melanin adequately (Table 23.1).

OCULOCUTANEOUS ALBINISM TYPE 1

Oculocutaneous albinism type 1 (OCA1) is the second most common OCA worldwide.

Cutaneous findings

In OCA1A, there is marked generalized hypopigmentation at birth, with white hair and skin (Figs. 23.1, 23.2). As the child

matures, the skin remains white. Nevus are not pigmented and sun tanning does not occur. The hair may acquire a slightly yellowish tint as a result of denaturing of hair keratins.

In OCA1B, the variable decrease in tyrosinase activity results in several clinical phenotypes: yellow, minimal pigment, platinum, and temperature-sensitive. Individuals with OCA1B form pheomelanin, which requires less tyrosinase activity, and this results in some pigment production during the first two decades of life.⁴ Affected individuals have a similar appearance to those with OCA1A at birth, but with time develop some pigment. Hair color can change from white to light blond and even progress to light brown in adolescence. With sun exposure, some individuals with OCA1B may be able to tan, although it is more common to burn without tanning. Pigmented nevi and freckles may develop.⁵

An interesting subtype of OCA1B is the temperature-sensitive phenotype in which the tyrosinase activity is seen mainly on the extremities. In these patients, the enzyme has no activity at 37°C, but some activity at 35°C. These individuals have white or lightly pigmented hairs on the scalp and trunk (axillae, pubic area) and darkly pigmented hair peripherally (legs, arms). The pattern is similar to that observed in Siamese cats.⁴

Extracutaneous findings

In OCA1A, the irises are pale blue at birth and throughout life. In bright light, the entire iris can appear pink or red, which is caused by its translucency.⁵ Severe photophobia results from a lack of retinal pigment. Other ocular abnormalities include decreased visual acuity, nystagmus, and strabismus.

In OCA1B, the irises can progressively darken to light tan or brown. In both subtypes, vision may remain stable or deteriorate with age.

Etiology and pathogenesis

OCA1 is caused by loss-of-function mutations in the tyrosinase gene (*TYR*), which is mapped to chromosome 11q14.3. Tyrosinase is the key enzyme that catalyzes the first two steps in melanin synthesis, converting tyrosine to L-DOPA (L-3,4-dihydroxyphenylalanine), and L-DOPA to DOPAquinone. The OCA1A subtype is characterized by mutations that result in complete loss of tyrosinase activity, whereas OCA1B is caused by mutations that result in markedly reduced tyrosinase activity (5–10% of the normal level).

OCULOCUTANEOUS ALBINISM TYPE 2

Oculocutaneous albinism type 2 (OCA2) is the most common form of OCA. It is most prevalent in people of African descent.⁶

Cutaneous findings

There is a spectrum of clinical phenotypes, depending on the ethnic background and the dilution of hair and skin pigment,

BOX 23.1 HYPOPIGMENTARY DISORDERS IN NEONATES AND INFANTS**GENERALIZED HYPOPIGMENTATION INVOLVING SKIN, HAIR AND EYES**

- Oculocutaneous albinism
- Hermansky–Pudlak syndrome
- Chediak–Higashi syndrome
- Cross syndrome
- Metabolic disorders
 - Phenylketonuria
 - Histidinemia
 - Homocystinuria

GENERALIZED HYPOPIGMENTATION INVOLVING SKIN AND HAIR

- Griscelli syndrome
- Elejalde syndrome
- Menkes disease and occipital horn syndrome

MOSAIC HYPOPIGMENTATION

- Nevoid hypopigmentation (hypomelanosis of Ito)
- Nevus depigmentosus

LOCALIZED HYPOPIGMENTATION

- Piebaldism
- Waardenburg syndrome
- Tuberous sclerosis complex
- Nevus anemicus
- Vitiligo
- Post-inflammatory hypopigmentation
- Congenital halo nevi

MISCELLANEOUS HYPOPIGMENTATION

- Alezzandrini syndrome
- Ziprkowski–Margolis syndrome



Figure 23.1 OCA1A. Generalized hypopigmentation, including snow-white hair at birth.



Figure 23.2 OCA1A. Infant of African descent with diffuse skin and hair hypopigmentation.

which may be minimal to moderate. Comparison with a first-degree relative may be necessary to distinguish the degree of lightening.⁴ Most individuals are born with creamy white skin, and light yellow or blond hair. Depending on the individual's ethnic background, hair may also be reddish blond or brown. Pigmented birthmarks may be present. With maturity, the amount of pigment in the skin and hair tends to increase. In sun-exposed areas, pigmented nevi and freckles can develop.

Extracutaneous findings

The dilution of iris pigment may be mild to moderate. With age, the amount of pigment in the eyes tends to increase. Ocular manifestations are generally not as severe as those seen in OCA1A.² Visual acuity and nystagmus tend to improve with age.

OCA2 can be found in 1% of individuals with Prader–Willi and Angelman syndromes.⁶

Etiology and pathogenesis

OCA2 results from loss-of-function mutations of the *OCA2* gene (previously called the *P* gene), which is mapped to chromosome 15q11.2–q13.⁷ The *OCA2* gene encodes the P protein, a melanosomal membrane protein. The specific function of the P protein is currently not known, but is believed to be involved in tyrosine transport within the melanocyte, regulation of melanosome pH and tyrosinase processing and transport.⁸ The melanocytes of affected individuals are able to synthesize some melanin, but the majority is yellow pheomelanin rather than black-brown eumelanin.

Prader–Willi syndrome involves deletions of the 15q region, including the *OCA2* gene, on the paternally inherited copy of chromosome 15, whereas Angelman syndrome involves loss of the maternally inherited allele. Deletion of one copy of the *OCA2* gene associated with a mutation in the second copy results in OCA2 in these patients.⁶

OCULOCUTANEOUS ALBINISM TYPE 3

OCA3, previously called 'rufous OCA', is most commonly seen in people of African and Puerto Rican descent.^{9,10}

TABLE 23.1 Classification of disorders with cutaneous and ocular albinism

	OCA1A Tyrosinase negative	OCA1B Tyrosinase positive	OCA2 Tyrosinase positive	OCA3 Rufous	OCA4	HPS	CHS
Skin color	White	White at birth, develops some pigmentation in first and second decades	Creamy white to brown at birth. Slight darkening with age	Light brown to red-brown	Creamy white to brown at birth. Slight darkening with age	White to brown	Creamy white to slate gray
Pigmented nevi and freckles	Absent	Present	Present	Absent	Present	Many in exposed areas	Present
Hair color	White throughout life; may become light yellow	White to light yellow at birth; turns yellow or blond in first few years	Light yellow, blond to brown at birth; may darken with age	Light brown to red-brown. May darken with age	Silvery white to light yellow at birth. May darken in childhood	White, blond to brown	Blond to light brown; metallic silver-gray sheen
Gene (mapping), function	TYR (11q14.3) Encodes tyrosinase	TYR (11q14.3) Encodes tyrosinase	OCA2 (15q11.2-q12) Encodes P protein, a melanosomal membrane protein	TYRP1 (9q23) Encodes dihydroxyindol carboxylic acid oxidase, a melanogenic enzyme	SLC45A2 (5p13.2) Encodes membrane-associated transporter protein	HPS1: HPS1 (10q24.2) HPS2: AP3B1 (5q14.1) HPS3: HPS3 (3q24) HPS4: HPS4 (22q12.1) HPS5: HPS5 (11p15.1) HPS6: HPS6 (10q24.32) HPS7: DTNBP1 (6p22.3) HPS8: BLOC1S3 (19q13.32) HPS9: PLDN (15q21.1) Encode proteins involved in biogenesis of lysosomes and lysosome-related organelles, such as melanosomes and platelet-dense granules. Some may play a role in intracellular vesicle trafficking	LYST (1q42.3) Encodes lysosomal-traffic regulator, a cytoplasmic protein which may function as an adapter protein that mediates intracellular membrane fusion reactions
Mouse model	Albino	Albino	Pink-eye dilution	Brown	Underwhite	HPS1: Pale-ear HPS2: Pearl HPS3: Cocoa HPS4: Light-ear HPS5: Ruby eye 2 HPS6: Ruby eye HPS7: Sandy HPS8: Reduced pigmentation	Beige
Hair bulb melanosomes	Stages I, II	Stages I, II, III	Stages I, II, III	Stages I, II, III, IV	Stages I, II, III	Stages I, II, III	Macromelanosomes and normal to Stage IV

HPS, Hermansky-Pudlak syndrome; CHS, Chediak-Higashi syndrome.

Cutaneous findings

At birth, individuals with this tyrosinase-positive OCA have light brown to red-brown skin and hair. With age, the hair becomes more pigmented. Mild sun tanning is possible.

Extracutaneous findings

At birth, the irises are light brown and become more pigmented with age. Ocular manifestations are present, but less severe. Red reflex on transillumination of the iris and nystagmus are important clues to the diagnosis in dark-skinned people.

Etiology and pathogenesis

OCA3 is due to loss-of-function mutations of tyrosinase-related protein-1 gene (*TYRP1*), which is mapped to chromosome 9q23.¹¹ The *TYRP1* gene encodes dihydroxyindolcarboxylic acid oxidase, a melanogenic enzyme essential for eumelanin synthesis.¹²

OCULOCUTANEOUS ALBINISM TYPE 4

OCA4 may be one of the most common types of OCA in Japan, with solute carrier family 45, member 2, *SLC45A2* (previously called 'membrane-associated transporter protein', *MATP*) gene mutations found in 24% of 75 unrelated Japanese patients with OCA.¹³

Cutaneous findings

The phenotype resembles that of OCA2 and the range of skin pigmentation is broad, from creamy white to brown.^{14,15} The hair is silvery white to light yellow at birth, and may darken in childhood.

Extracutaneous findings

Ocular manifestations include nystagmus, decreased iris pigment with iris translucency, reduced retinal pigment, foveal hypoplasia associated with reduction in visual acuity, and strabismus.

Etiology and pathogenesis

OCA4 results from mutations in the *SLC45A2* gene, which is mapped to chromosome 5p13.2. The gene encodes a melanosomal membrane protein that is likely to function as a transporter.¹³ The similar functions of the *OCA2* and *SLC45A2* genes may explain the phenotypic resemblance of OCA2 and OCA4.

Differential diagnosis

The diagnosis of OCA is usually made clinically and can be confirmed by DNA mutation analysis. Historically, the hair bulb incubator test for tyrosinase activity was used to differentiate between tyrosinase-positive and tyrosinase-negative OCA. In tyrosinase-negative albinism, there is the lack of pigment formation in hair bulbs when incubated with tyrosine, whereas in tyrosinase-positive albinism, pigment is produced. Prenatal diagnosis of OCA using DNA mutation analysis is available.

OCA can be differentiated from other disorders with cutaneous and ocular albinism by the absence of neurological defects, immunodeficiency, and bleeding diathesis.

Treatment and care

No specific treatment is available for OCA. The importance of photoprotection, including sun avoidance, broad-spectrum

sunscreen, protective eyewear and clothing, should be stressed to reduce the risk of photodamage and cutaneous malignancies. Early ophthalmologic evaluation and management is important. As squamous cell carcinomas and basal cell carcinomas have been known to develop in all types of OCA, yearly examination by a dermatologist is recommended.

HERMANSKY-PUDLAK SYNDROME

Hermansky-Pudlak syndrome (HPS) comprises nine genetically different autosomal recessive disorders characterized by tyrosinase-positive OCA, a bleeding diathesis, and a lysosomal ceroid storage disease affecting the viscera.^{16–18} The majority of individuals affected are of Puerto Rican or Dutch descent. HPS type 1 is the most common.

Cutaneous findings

The degree of pigmentary dilution in the skin and hair is highly variable. The color of the skin and hair ranges from white to brown.

Extracutaneous findings

The degree of pigmentary dilution in the eyes is highly variable. Other ocular findings include nystagmus, reduced retinal pigment, and foveal hypoplasia with significant reduction in visual acuity. The nystagmus is most obvious during periods of fatigue or emotional change. The bleeding diathesis is caused by platelet storage pool deficiency and results in epistaxis, gingival, menstrual, colonic or post-surgical bleeding. Platelet numbers, prothrombin time, and partial thromboplastin time are normal but bleeding time is prolonged. The absence of dense bodies on electron microscopy of platelets is pathognomonic of HPS.¹⁹ Lysosomal ceroid accumulation can result in interstitial pulmonary fibrosis, granulomatous colitis, cardiomyopathy, and renal failure. These life-threatening complications usually develop in adulthood. Some patients with HPS type 2 have persistent neutropenia and suffer from recurrent bacterial infections.^{20,21}

Etiology and pathogenesis

Most of the HPS-related genes encode proteins involved in the biogenesis of lysosome-related organelles. Ceroid is produced by degradation of lipids and glycoproteins within lysosomes. Ceroid accumulation in HPS suggests a defect in the elimination mechanisms of lysosomes.²²

Differential diagnosis

The diagnosis of HPS is made on clinical findings of oculocutaneous albinism, bleeding diathesis, and absence of dense bodies on electron microscopy of platelets. Molecular genetic testing of some HPS types, e.g. HPS1, HPS3, is available on a clinical basis. The differential diagnosis includes the Griscelli, Elejalde and Cross syndromes.

Treatment and care

Photoprotection is important, as patients have a predisposition to develop basal cell carcinoma and squamous cell carcinoma. An examination by a dermatologist should be performed annually. Patients should avoid aspirin and trauma to minimize the chance of a bleeding episode. Platelet transfusions may be considered prior to surgical procedures. Cigarette smoking should

be avoided, as this reduces pulmonary function and may hasten progression of pulmonary fibrosis.

CHEDIAK–HIGASHI SYNDROME

Chediak–Higashi syndrome (CHS) is an autosomal recessive disorder characterized by OCA, immunodeficiency, progressive neurological deterioration, a mild bleeding tendency and abnormal inclusions present in a wide variety of cells.

Cutaneous findings

Compared with unaffected family members, the skin and the hair of affected individuals are lighter in color. Cutaneous pigmentation is often slightly to moderately decreased. The hair is blond to light brown, often with a silvery tint (Fig. 23.3). Recurrent skin and systemic pyogenic infections occur in early childhood. Cutaneous involvement usually manifests as a pyoderma, and there are a few reports of deeper involvement resembling pyoderma gangrenosum.²³

Extracutaneous findings

Loss of ocular pigmentation results in a translucent iris and pale retina, leading to photophobia and an increased red reflex. Visual acuity is normal, but strabismus and nystagmus are common.

Infections typically involve the skin, lungs, and upper respiratory tract. These intractable infections are often fatal before the age of 10 years. Common culprits include *Staphylococcus aureus*, *Streptococcus pyogenes* and *S. pneumoniae*.

Periodontitis is an important manifestation of the immunologic dysfunction.²⁴

Progressive neurologic deterioration with clumsiness, abnormal gait, paresthesias, and dysesthesias is often apparent later in childhood. Other neurologic abnormalities include peripheral and cranial neuropathies, spinocerebellar degeneration,

ataxia, seizures, decreased deep tendon reflexes, cranial nerve palsies, and motor weakness.^{25–30}

Most patients with CHS eventually develop a lymphoproliferative syndrome ('accelerated phase') characterized by fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, bleeding, and generalized lymphohistiocytic infiltrates.²⁶ Viral infections, particularly with the Epstein–Barr virus, have been implicated in causing the accelerated phase.^{31,32}

Etiology and pathogenesis

CHS results from mutations in the lysosomal trafficking regulator gene (*LYST*) gene. The *LYST* gene (1q 42.1–q42.2) encodes a large cytoplasmic protein that appears to function as an adapter protein to mediate intracellular membrane fusion reactions.³³

Natural killer (NK) cell function is drastically decreased. Diminished chemotaxis of granulocytes, monocytes, and lymphocytes has also been reported, as well as decreased antibody-dependent cytotoxicity and reduced suppressor T-cell function.^{34–36} The resulting susceptibility to infections is caused by the combination of these factors.³⁷

The diagnostic hallmark of CHS is the finding of giant lysosomal granules within leukocytes, melanocytes, platelets, and other cells due to uncontrolled fusion of lysosomes. In bone marrow myeloid cells, the giant granules appear prominent. In melanocytes, giant melanosomes result from uncontrolled fusion of melanosomes, and this failure to disperse melanin to adjacent keratinocytes accounts for the decrease in pigmentation.³⁸ On a cellular level, abnormal intracellular transport to and from the lysosomes has been detected.³⁹ Giant granules within the phagocytic cells cannot discharge their lysosomal and peroxidative enzymes into phagocytic vacuoles.⁴⁰ Prenatal diagnosis has been successfully performed using light microscopy by examining fetal hair shafts for characteristic clumping of melanosomes.⁴¹

Treatment and care

Hematopoietic stem-cell transplantation (HSCT) is the only definitive treatment for this disorder.⁴² The NK cell defects and immunodeficiencies can be reversed, but the neurological deterioration and pigmentary dilution are not altered.^{43,44}

Without allogeneic HSCT, patients who develop an accelerated phase usually die in childhood, usually from pyogenic infections or hemorrhage.²⁶ Patients who do not develop an accelerated phase tend to have fewer or no infections, but usually develop progressively debilitating neurologic manifestations.^{45,46} Supportive treatments in early infancy include antibiotics for infections, and intravenous γ -globulin. Nonsteroidal anti-inflammatory drugs can exacerbate the bleeding tendency and should be avoided. Ascorbic acid has been shown to partially correct the granulocytic function in some patients.^{34,35}

CROSS SYNDROME

Cross syndrome, or oculocerebral syndrome with hypopigmentation, is an oculocutaneous albinism associated with ocular anomalies, postnatal growth retardation, and neurological defects.^{47–49} The inheritance is probably autosomal recessive.

Cutaneous findings

The affected neonate has cutaneous generalized hypopigmentation and silvery hair.



Figure 23.3 Chediak–Higashi syndrome. The hair displays a silvery sheen.

Extracutaneous findings

Ocular defects include microphthalmos, a small opaque cornea, and nystagmus. Neurological defects include mental retardation, ataxia, and spasticity.

Treatment and care

Treatment is supportive.

PHENYLKETONURIA (PHENYLALANINE HYDROXYLASE DEFICIENCY)

Phenylketonuria (PKU) is an autosomal recessive disorder that results from the impaired conversion of phenylalanine to tyrosine, which is caused by the absence of hepatic phenylalanine hydroxylase (PAH) activity. The absence of this enzyme leads to a build-up of the amino acid phenylalanine and its byproducts in the bloodstream and spinal fluid. The incidence in the USA is estimated at 1 in 10 000 among Caucasians.⁵⁰ It is most commonly observed in individuals of Scandinavian, Turkish and Irish descent, with males and females equally affected. PKU without treatment results in mental retardation and oculocutaneous pigment dilution. Most affected individuals have blond hair, blue eyes, fair skin, photosensitivity, a musty body odor, and neurologic disturbances.⁵¹

Cutaneous findings

At birth, the neonate appears normal but may have a musty odor secondary to urinary and sweat phenylacetic acid or phenylacetaldehyde. Caucasian children with PKU almost invariably have blond hair, blue eyes, fair skin, and photosensitivity. African-American and Asian children tend to be lighter in color than their parents and unaffected siblings. The ability to tan is normal. Endogenous eczema often develops in these patients.

Extracutaneous findings

In affected babies, serum phenylalanine levels begin to rise on the third or fourth day of life. Newborn screening with the Guthrie card bacterial inhibition assay test was implemented in the USA beginning in 1963, testing all newborns for PKU. Prenatal diagnosis is also possible by performing amniocentesis or chorionic villus sampling, with identification of the gene.⁵¹ Untreated PKU results in neurologic defects, including mental retardation, seizures, psychosis, hyperreflexia, and growth retardation.

Etiology and pathogenesis

Phenylalanine hydroxylase deficiency is caused by mutations in the PAH gene (mapped to 12q23.2), with more than 400 different mutations identified so far.^{52,53} Hypotheses to account for the decrease in skin and hair pigmentation include a competitive inhibition of the binding of tyrosine to tyrosinase by excess phenylalanine or a decreased amount of tyrosine.⁵⁴

Treatment and care

With a low phenylalanine diet, the skin color, photosensitivity, odor, and eczema are reversible. Implementing a diet low in phenylalanine early in infancy can also dramatically reduce the mental retardation.⁵¹ Although children with treated PKU typically have a lower IQ than the general population, affected individuals can be expected to have a low-normal to normal

intelligence if blood phenylalanine is maintained at a reasonable level in early childhood.⁵⁵ Supplementation with tyrosine or tryptophan in the diet may be necessary. For women with PAH deficiency who are considering pregnancy, dietary restriction must be started before conception and continued throughout pregnancy.⁵⁶ Aspartame, an artificial sweetener that contains phenylalanine, should be avoided.

Generalized hypopigmentation involving skin and hair

GRISCELLI SYNDROME

Griscelli first described this syndrome in 1978.⁵⁷ It is a rare autosomal recessive syndrome that results in pigmentary dilution of the skin and hair, the presence of large clumps of pigment in hair shafts, and an accumulation of melanosomes in melanocytes. There are three types:

- Type 1 (GS1): association of hypopigmentation and neurological abnormalities, due to mutations of the *MYO5A* gene (15q21.2)^{58,59}
- Type 2 (GS2): association of hypopigmentation and immunological abnormalities, due to *RAB27A* gene (15q21.3) mutation⁶⁰
- Type 3 (GS3): only hypopigmentation, due to melanophilin (*MLPH*) gene (2q37.3) mutation.⁶¹

Cutaneous findings

In early childhood, individuals with all three types of GS have silvery gray hair, eyebrows, and eyelashes (findings that may also be present in the neonatal period), and skin hypopigmentation.^{62–65}

Histologically, the hair shafts reveal uneven clumps of melanin, mainly in the medulla. Skin biopsy specimens reveal hyperpigmented oval melanocytes and poorly pigmented adjacent keratinocytes. On electron microscopic examination, epidermal melanocytes are found to contain perinuclear stage IV melanosomes. Adjacent keratinocytes contain only sparse melanosomes.⁶⁶

Prenatal diagnosis of Griscelli syndrome has been accomplished by examination of hair from fetal scalp biopsies performed at 21 weeks' gestation, with confirmatory postabortion examination of the fetus revealing silvery hair and identical microscopic findings.⁴¹

Extracutaneous findings

Neurological defects in GS1 include intracranial hypertension, cerebellar signs, encephalopathy, hemiparesis, peripheral facial palsy, spasticity, hypotonia, seizures, psychomotor retardation, and progressive neurologic deterioration.^{64–68}

Immunological abnormalities in GS2 result in severe pyogenic infections, due to defective release of cytotoxic lysosomal contents from hematopoietic cells, and a hemophagocytic syndrome.^{66,69} There is combined T- and B-cell immunodeficiency. Frequent pyogenic infections, acute febrile episodes, neutropenia, and thrombocytopenia usually begin between 4 months of age and 4 years.^{57,64,65,67,70–72} The hemophagocytic syndrome is characterized by acute onset of uncontrolled lymphocyte and macrophage activation, resulting in infiltration and hemophagocytosis in multiple organs and death.

Etiology and pathogenesis

The *MYO5A*, *RAB27A* and *MLPH* genes encode respectively myosin 5a, rab27a and melanophilin, which form a complex that allows the transport of melanosomes on actin fibers and the docking of melanosomes on the dendritic tips.^{61,73,74}

Differential diagnosis

Differentiation from Chediak–Higashi syndrome can be made by pathognomonic light and electron microscopic features. Griscelli syndrome lacks the large cytoplasmic inclusions and granulocyte abnormalities that are characteristic of Chediak–Higashi syndrome. Both diseases, however, are associated with an accelerated phase and carry a poor prognosis without bone marrow transplantation.

Treatment and care

Bone marrow transplant is most successful when performed early in the course of disease.^{66,75}

ELEJALDE SYNDROME

Elejalde syndrome, also called neuroectodermal melanolyso-somal disease, is a rare autosomal recessive disorder characterized by silvery hair, hypopigmented skin, severe central nervous system dysfunction, and abnormal intracytoplasmic inclusions in fibroblasts, histiocytes, and lymphocytes.^{76–78}

Cutaneous findings

Neonates have silvery hair and generalized hypopigmentation of the skin, which may develop a bronze color after sun exposure.⁷⁹

In homozygotes, abnormal melanolysosomes are found in melanocytes and keratinocytes, cultured fibroblasts, and histiocytes of bone marrow.

Extracutaneous findings

Extracutaneous features include mental retardation, hypotonic facies, plagiocephaly, nystagmus, diplopia, micrognathia, crowded teeth, a narrow high palate, pectus excavatum, and cryptorchidism. Neurological abnormalities range from severe hypotonia and the almost complete absence of movements, to seizures and spasticity. The age of onset of neurologic signs ranges from 1 month to 11 years.⁷⁸

Differential diagnosis

Several authors have suggested that subtypes of Elejalde syndrome and Griscelli syndrome type 1 are the same entity.^{80–83} However, the absence of immunologic defects allows Elejalde syndrome to be distinguished from the Griscelli syndrome type 1. Chediak–Higashi syndrome should also be considered in the differential diagnosis.

Treatment and care

Treatment is supportive and prognosis is poor.

MENKES DISEASE (AND OCCIPITAL HORN SYNDROME)

Classic Menkes disease is a multisystem disorder that manifests with hypopigmentation, hair abnormalities, failure to thrive, connective tissue changes, seizures, neurological degeneration,

and death by the age of 3 years.⁸⁴ The disorder has a prevalence of 1 in 250 000–350 000 live births.⁸⁵ Most infants born with Menkes disease appear normal for the first few months of life before showing a rapid decline in growth and neurologic development.

Cutaneous findings

The cutaneous manifestations include alterations in hair, pigmentation, and elasticity of the skin.⁸⁶ The scalp hair may appear normal at birth, but by about 3 months of age, it becomes sparse, light colored, lusterless, with a 'steel wool' quality. The hair is fragile and fractures easily, resulting in generalized alopecia (Fig. 23.4). Pili torti is the most common hair shaft abnormality (Fig. 23.5), demonstrating a flattened appearance under light microscopy with multiple twists of 180° around the long



Figure 23.4 Sparse, short, hypopigmented hair in Menkes disease. (Reproduced with permission from Schachner L, Hansen R. *Pediatric dermatology*. 3rd ed. Edinburgh: Mosby; 2003.)

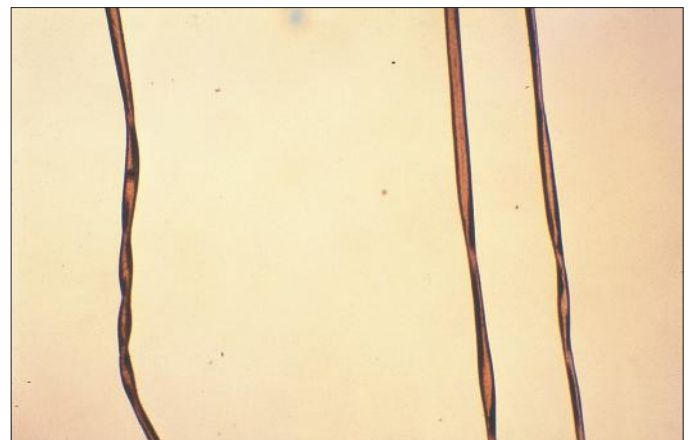


Figure 23.5 Light microscopy showing pili torti. (Reproduced with permission from Schachner L, Hansen R. *Pediatric dermatology*. 3rd ed. Edinburgh: Mosby; 2003.)



Figure 23.6 Lax skin in the groins and on the thighs. (Reproduced with permission from Peterson J, Drolet BA, Esterly NB. *Pediatr Dermatol* 1998; 15:137–139.)

axis of the shaft.⁸⁷ The twisted hairs result from excessive free sulfhydryl groups and a decrease in copper-dependent disulfide bonds. Cutaneous hypopigmentation is common, may be generalized or localized to the skin folds, and is caused by decreased tyrosinase, a copper-containing enzyme. Scaly dermatitis in a seborrheic distribution occurs frequently⁸⁸ and transient neonatal erythroderma has been reported as an initial manifestation of Menkes disease.⁸⁹ The skin is lax, and this doughy laxity is most prominent over the posterior neck, eyebrows, and leg folds (Fig. 23.6).⁸⁶ Generalized puffiness of the cheeks and feet has been noted.

Extracutaneous findings

Progressive neurodegeneration begins at about 2 months of age as a result of gliosis and demyelination of the cerebrum and cerebellum.⁸⁴ Patients present with seizures, hypothermia, developmental retardation, spontaneous subdural hematomas, muscle hypotonia, and feeding difficulties.⁹⁰ Urogenital problems include undescended testes, hydronephrosis, hydro-ureter, recurrent urinary tract infections, diverticula of the ureters and bladder, and rupture of the bladder. Chronic intractable diarrhea resulting in malnutrition^{88,91} and increased frequency of congenital heart defects are seen.⁹² Skeletal abnormalities are manifested as wormian bones of the skull and spurring of long bone metaphyses. Connective tissue changes are evidenced by loose joints and tortuous blood vessels, such as the carotid and cerebellar arteries, which may cause intracranial hemorrhages. This increased tortuosity is secondary to fragmentation of the internal elastic lamina of the arteries. Low copper and ceruloplasmin levels in the serum and high copper levels in cultured fibroblasts are useful in the diagnosis.⁹³ Menkes disease can be considered a disorder of copper maldistribution.

Etiology and pathogenesis

Menkes disease and occipital horn syndrome are rare, allelic, X-linked recessive copper deficiency disorders caused by mutations in the *ATP7A* gene (mapped to Xq21.1), which encodes a copper-transporting P-type ATPase involved in transport of copper to copper-requiring proteins.^{94,95} ATPase is localized in the trans-Golgi membrane of cells. The clinical features are due

TABLE 23.2

Effects of defective copper-dependent enzymes in Menkes disease

Clinical manifestations	Defective enzyme (function)
Connective tissue abnormalities: Laxity of skin and joints Vascular abnormalities Bony abnormalities Bladder diverticulae	Lysyl oxidase (cross-linkage of collagen and elastin)
Hypopigmentation	Tyrosinase (production of melanin)
Coarse, sparse brittle hair	Cross-linkase (cross-linkage of keratin)
Degeneration of myelin: seizures and spasticity	Superoxidase dismutase (detoxification of free radicals)
Deficient energy production: myopathy, ataxia, seizures	Cytochrome C oxidase (electron transport)
Hypothalamic imbalances: hypothermia, dehydration, hypotension, somnolence	Dopamine β hydroxylase (production of catecholamines)

to malfunction of one or more copper-requiring enzymes, such as lysyl oxidase, tyrosinase, cytochrome C oxidase, and dopamine beta-hydroxylase, caused by the deficiency of the *ATP7A* protein (Table 23.2).⁸⁶ Most patients are males, although a few female patients have also been reported. Most of the female patients have an X; autosome translocation, where the normal X-chromosome is preferentially inactivated.⁹⁶

Occipital horn syndrome, formerly classified as Ehlers–Danlos syndrome type IX or X-linked cutis laxa, is now recognized as a milder form of Menkes disease and is caused by mutations in the same gene. Occipital horn syndrome is characterized primarily by connective tissue abnormalities, including skin laxity, hyperextensible joints, urinary tract diverticuli, hernias, and bony changes such as osteoporosis, arthrosis, and exostoses, such as the presence of a spike of ossification within the occipital insertion of the paraspinal muscles trapezius and sternocleidomastoid muscles at their attachments to the occipital bone (occipital horns), which gives the syndrome its name.⁹⁷ Intelligence is normal or borderline, and patients can survive into adulthood. The milder phenotype results from the presence of low levels of functional *ATP7A*, unlike Menkes disease, in which no normal *ATP7A* activity exists.^{85,98}

Treatment and care

Daily subcutaneous administration of copper-histidine has been shown to be helpful in preventing the severe neurodegenerative problems in some patients with Menkes disease when the treatment is initiated early in life before the onset of significant neurological symptoms.^{99,100} This treatment, however, does not prevent the development of connective tissue problems, and cannot be regarded as a cure for Menkes disease.^{100–102}

Mosaic hypopigmentation

Mosaicism refers to the presence of two or more genetically distinct cell lines within an individual. These cell lines may be due to X-inactivation, as is normal in all human females, or to postzygotic somatic mutation. When mosaicism affects the skin, the affected skin may show patchy hypopigmentation or hyperpigmentation in a linear or segmental distribution



Figure 23.7 Nevoid hypopigmentation. Whorls and streaks of macular hypopigmentation following lines of Blaschko.

(Figs. 23.7, 23.8). (Pigmentary mosaicism associated with hyperpigmented disorders is discussed in [Chapter 24](#), and other mosaic conditions in [Chapter 29](#).) Segmental hypopigmented lesions may be seen as an isolated cutaneous skin condition or as part of a genetic syndrome. The presence of mosaicism can sometimes be documented by the karyotyping of lymphocytes from peripheral blood or by genomic evaluation of both involved and uninvolved skin.

In 1901, Blaschko characterized the distribution of segmental and linear skin abnormalities by examining patients with linear lesions and formulating a patterned composite diagram. He described these patterns as V-shaped or fountain-like over the spine, S-shaped or whorled on the anterior and lateral aspects of the trunk, and linear over the extremities (see [Chapter 3](#)). These lines should not be confused with dermatomes, which



Figure 23.8 Nevoid hypopigmentation without systemic anomalies. This child was otherwise well.

are the segments of skin that correspond to sensory innervation.¹⁰³ Hypopigmentation that follows the lines of Blaschko and segmental patterns is thought to reflect cellular migration during embryogenesis affecting pigmentation.¹⁰⁴

NEVOID HYPOPIGMENTATION

In 1952, a Japanese dermatologist named Ito described a 21-year-old woman with hypopigmented cutaneous whorls and streaks.¹⁰⁵ As the distribution of the hypopigmentation was analogous to that of the hyperpigmented streaks observed in incontinentia pigmenti, he called the disorder 'incontinentia pigmenti achromians'. To avoid confusion of these two unrelated entities, the preferred terminology later became 'hypomelanosis of Ito' (HI).¹⁰⁶

HI is a descriptive term, rather than a diagnosis.¹⁰⁷ It has been used for a phenotype with unilateral or bilateral hypopigmented streaks and whorls that follow the lines of Blaschko and which are present at birth or become apparent within the first 2 years of life (Figs 23.7, 23.8).¹⁰⁸ There may be associated systemic findings.

Recently, the terms 'nevoid hypopigmentation,' 'mosaic hypopigmentation' or 'segmental pigmentary disorder' with or without systemic anomalies, were adopted to better reflect the heterogeneous nature of this group of disorders.

Cutaneous findings

Hypopigmented whorls and streaks are distributed along the lines of Blaschko. They tend to be stable, although there are reported cases in which the pigmentary changes become more or less pronounced over time.¹⁰⁹ In some cases, both hypopigmented and hyperpigmented streaks are evident. Wood's lamp examination may help to determine the extent of the lesions in fair-skinned patients.

Extracutaneous findings

Extracutaneous findings are variable, and include central nervous, musculoskeletal, and/or ocular abnormalities.¹¹⁰ Defects of teeth, hair, nails, and sweat glands, as well as aplasia cutis, fibromas, and generalized or focal hypertrichosis, have been reported.^{109,111,112} Additional abnormalities reported include limb-length discrepancies, facial hemiatrophy, scoliosis, sternal abnormalities, dysmorphic facies, genitourinary and cardiac anomalies. Nearly all of the defects are detectable by a thorough physical examination and regular follow-up. Infants should be observed for evidence of CNS involvement, reflected by developmental delay or seizures.¹⁰⁹ Most children with CNS involvement manifest with neurological abnormalities before 2 years of age.

Etiology and pathogenesis

Embryonic somatic mutations are the likely pathogenesis, with distribution and pattern of lesions determined by the type of progenitor cell affected and the timing of mutation during embryogenesis. Multiple chromosomal abnormalities have been associated with HI, and most cases are sporadic and have negligible risk of recurrence.^{106,111,113} On histologic examination, the hypopigmented areas have either normal or reduced numbers of melanocytes, and those melanocytes that are present demonstrate a reduction in the number of melanosomes.¹¹⁴

Differential diagnosis

This includes nevus depigmentosus (also known as nevus achromicus) and Goltz syndrome. Patients with Goltz syndrome have both hyper- and hypopigmentation, as well as depressed areas of depigmentation following Blaschko's lines.

Treatment and care

Cosmetic cover-up products can be used to conceal the hypopigmented areas but are usually not needed. The use of sunscreens can prevent or lessen the accentuation of pigmentary differences.¹⁰⁹

NEVUS DEPIGMENTOSUS

Cutaneous findings

Nevus depigmentosus (nevus achromicus) is an uncommon birthmark occurring in 0.4% of newborns.¹¹⁵ It is a well-circumscribed area of hypopigmentation with an off-white color that may occur as a small isolated (circular or rectangular) patch, or develop in a unilateral segmental distribution or follow the lines of Blaschko.¹¹⁶ Hair within a nevus depigmentosus may also be hypopigmented, and the margins may be irregular or serrated. The isolated form is the most common (Fig. 23.9) and the lesions do not usually cross the midline.¹¹⁷ The term depigmentosus is a misnomer because the lesions are actually hypopigmented, not completely depigmented, and become more prominent under Wood's lamp. They are usually present at birth or become evident shortly thereafter, and remain stable in size and shape. Increase in size is in proportion to the growth of the child. Some lesions may appear during the first 3 years of life,^{117–119} with the trunk being the most commonly affected site.^{117,119,120} Occasionally, lesions may appear after the age of 3 years.^{117,120} In particular, the back and buttocks are most commonly affected, followed by the chest and abdomen.¹¹⁷ Males and females are affected equally and there is



Figure 23.9 Nevus depigmentosus. Well-circumscribed hypopigmented patch on the cheek that was present at birth.

no distinct pattern of inheritance.¹¹⁶ The hypothesis is that during embryogenesis a clone of cells with a reduced melanogenic potential arises via a post-zygotic somatic mutation.¹⁰³

Extracutaneous findings

Systemic manifestations are rare in patients with nevus depigmentosus. Neurologic abnormalities such as seizures and mental retardation have been reported,¹²¹ as well as ipsilateral hypertrophy of the extremities.¹²² In a survey of 50 patients with nevus depigmentosus, none had any extracutaneous features on examination.¹²³ In two studies involving 29 patients with nevus depigmentosus, extracutaneous abnormalities were present in about 10% of the children.^{118,124} Occasionally, lentigines can develop within the achromic nevi, and this could be explained by the reversion of a mutation in one of the genes involved in pigmentation.^{125,126} There is a report of an infant developing multiple primary milia within a nevus depigmentosus.¹²⁷

Etiology and pathogenesis

With dopa-staining, normal melanocytes are seen in nevus depigmentosus, and electron microscopic studies suggest a reduced synthesis of melanosomes and also a defect in their transfer to the keratinocytes, which could account for the hypopigmentation.¹²⁸ Transfer of melanosomes from melanocytes to keratinocytes is essential for normal pigmentation.

Differential diagnosis

Other entities with which nevus depigmentosus is sometimes confused include nevus anemicus, segmental vitiligo, hypopigmented lesions of tuberous sclerosis, and hypomelanosis of Ito. The distinction between nevus depigmentosus and hypomelanosis of Ito may be artificial, as many patients with segmental hypopigmented macules also have linear pigmentary anomalies, similar to those seen in hypomelanosis of Ito, and underlying mosaicism is the common factor.¹⁰⁹ Patients currently diagnosed with either of these conditions might simply be categorized as having nevoid hypopigmentation with or without extracutaneous anomalies. Genetic analysis may be considered

in all patients with segmental or linear pigmentary abnormalities, and those with extracutaneous abnormalities to investigate cytogenic anomalies.¹⁰⁹

Treatment and care

There has been a report of spontaneous resolution of nevus depigmentosus after a 6-year period.¹²⁹ One patient with a nevus depigmentosus had partial repigmentation following autologous melanocyte grafting.¹³⁰ The use of noncultured epidermal cellular grafting has been reported to be successful in the treatment of nevus depigmentosus and a mottled repigmentation of 78% was observed.¹³¹ Repigmentation however, may not be permanent and recurrence of a successfully repigmented nevus depigmentosus 6 years after blister roof grafting has been noted.¹³² Twice weekly narrow-band UVB for 32 sessions was helpful in repigmenting a nevus depigmentosus lesion,¹³³ as was the 308 nm excimer laser.¹³⁴ Cosmetic camouflage may be helpful.

Localized hypopigmented disorders

PIEBALDISM

Piebaldism is an autosomal dominant condition caused by defective cell proliferation and migration of melanocytes during embryogenesis.

Cutaneous findings

Piebaldism is characterized by congenital depigmented white patches of skin and hair on the forehead, central chest and abdomen, upper arms and lower legs, with normally pigmented skin on the hands and feet (Fig. 23.10). A white forelock, which consists of a tuft of white hair over the midfrontal scalp is present in 80–90% of patients and is associated with depigmentation of the underlying scalp.¹³⁵ Additional findings include poliosis of the eyebrows and eyelashes. The presence of islands of normally pigmented and hyperpigmented macules within the depigmented patches is typical and aids in the clinical diagnosis.¹³⁶ The lesions are generally stable in size and increase in proportion to the growth of the child, although in some cases spontaneous contraction or expansion with the appearance of new hyperpigmented macules has been reported.^{137,138} Spontaneous repigmentation of leukoderma in sun-exposed areas such as the forehead or knees has been reported.¹³⁹

Light and electron microscopy studies show a complete absence of melanin and melanocytes in the epidermis and hair



Figure 23.10 Piebaldism.

bulbs in the areas of leukoderma and poliosis.¹²⁸ The hypermelanotic macules contain a normal number of melanocytes, but an abundance of abnormal melanosomes that are granular and spherical in shape.

Extracutaneous findings^{140–144}

Piebaldism is not typically associated with abnormalities of other organs, although associated mental retardation has been reported.¹⁴⁰ This may represent contiguous gene deletion syndromes, with inclusion of the *KIT* gene responsible for piebaldism as well as nearby genes whose absence result in neurologic deficits. There have been at least five reports of piebaldism associated with neurofibromatosis type 1 (NF1).^{141–144} Whether the simultaneous occurrence of these two dominantly inherited diseases is more than chance remains to be established. It has been suggested that café-au-lait macules and intertriginous freckling are occasional features of piebaldism itself and that the diagnosis of NF1 must be based on non-pigmentary diagnostic criteria such as neurofibromas or the presence of an NF1 gene mutation by DNA testing.^{145,146}

Etiology and pathogenesis

Piebaldism results from mutations of the *KIT* gene on chromosome 4q11–q12.¹⁴⁷ This codes for the tyrosine kinase transmembrane cellular receptor for mast/stem cell growth factor, a critical factor for melanoblast migration, proliferation, differentiation, and survival. The *KIT* proto-oncogenes consist of an extracellular ligand-binding domain, a transmembrane domain, and a cytoplasmic tyrosine kinase domain.¹⁴⁸ The severity of the clinical phenotype in piebaldism correlates with the site of the mutation within the *KIT* gene.^{149,150} The most severe mutations tend to be dominant negative missense mutations involving the intracellular tyrosine kinase domain. Mutations causing an intermediate severity phenotype have largely been located at the transmembrane region, and the mildest phenotypes are those that occur in the amino terminal extracellular ligand-binding domain. It has been shown that *KIT* activation induces the expression of a zinc-finger neural crest transcription factor SLUG, and that SLUG is necessary for the normal development of melanocytes, hematopoietic stem cells, and germ cells.¹⁵¹ It has also been shown that deletions in the SLUG (*SNA12*) gene on chromosome 8q11 are responsible for some cases of piebaldism that lacked mutations in *KIT*.¹⁵²

Differential diagnosis

Disorders with similar clinical presentations are vitiligo and Waardenburg syndrome. Vitiligo is acquired later in life, tends to progress, and has a different distribution. Waardenburg syndrome is the major entity in the differential diagnosis of piebaldism, and the patient should be examined for evidence of facial dysmorphism, heterochromia of the irides, and congenital sensorineural hearing loss.

Treatment and care

Photoprotection of the depigmented patches is important, beginning early in life to protect the amelanotic areas from burning with sun exposure and to avoid skin cancers later on. Cosmetic camouflage or the use of a pigmenting tanning product such as dihydroxyacetone to camouflage the depigmented lesions are useful, although temporary.¹⁵³ PUVA therapy is generally disappointing,¹⁵⁴ but a combination of dermabrasion and split-thickness skin grafting followed by minigrafting¹⁵⁵

or the use of autologous cultured epidermal grafts¹⁵⁶ may be worthwhile in selected patients. Recently, the use of noncultured epidermal cellular grafting¹³¹ and melanocyte transplant techniques using noncultured melanocytes (minigrafting)¹⁵⁷ has been shown to be helpful with high repigmentation rates.

WAARDENBURG SYNDROME

Waardenburg syndrome is a rare autosomal dominant disorder characterized by depigmented patches of the skin and hair, heterochromia iridis, congenital nerve deafness, and craniofacial anomalies. It is caused by the absence of melanocytes in the skin, hair, eyes, and stria vascularis of the cochlea, and is classified as a disorder of neural crest development.¹⁵⁸

The estimated incidence of Waardenburg syndrome is 1 in 42 000 in the Netherlands¹⁵⁹ and 1 in 20 000 in Kenya.¹⁶⁰ It accounts for between 2% and 5% of cases of congenital deafness.¹⁶¹ Both sexes and all races are equally affected.¹⁶² Four types of Waardenburg syndrome have been described on clinical and genetic grounds (Box 23.2).

Cutaneous and extracutaneous findings

Affected persons have a depigmented patch, often V-shaped, on the central forehead in association with a white forelock.¹⁵⁹ Premature graying of the hair may occur. Depigmented patches with irregular borders containing hyperpigmented macules, resembling piebaldism, as well as hyperpigmented macules on normal skin, have been described.¹⁶² Histology reveals a reduced

number or complete absence of melanocytes within the depigmented areas.¹⁶³ Synophrys, or fusion of the medial eyebrows, is typical in Waardenburg syndrome. Heterochromia irides, or differently colored irises, may be present, as well as sectorial areas of diminished pigment in a single iris and bilateral isohypochromia iridis (pale blue eyes) (Fig. 23.11).¹⁶⁴ Type 1 Waardenburg syndrome is characterized by the presence of dystopia canthorum, or an increase in the inner canthal distance, without change in the interpupillary distance. If the inner canthal distance divided by the interpupillary distance exceeds 0.6, dystopia canthorum is present.¹⁶⁴ In type 2 Waardenburg syndrome, dystopia canthorum is absent.¹⁶⁵ Additional facial features include a broad nasal root, hypoplastic alar cartilage, a thin upper lip and a protuberant lower lip.¹⁵⁹

Congenital sensorineural hearing loss is a hallmark of all forms of Waardenburg syndrome and may be unilateral or bilateral.^{159,165} Histopathologic examination of the inner ears has shown absent organs of Corti, atrophy of the spiral ganglion, and reduction of nerve fibers.¹⁶⁶ Hearing loss and heterochromia irides are more common in type 2 than in type 1 Waardenburg syndrome.¹⁶⁷ Rarely cleft lip and palate¹⁶⁸ and neural tube defects such as spina bifida¹⁶⁹ have been reported in association with Waardenburg syndrome.

Waardenburg syndrome type III (Klein–Waardenburg syndrome) is similar to type 1, but is also accompanied by musculoskeletal anomalies of upper limbs and pectoral areas.¹⁷⁰ Type IV Waardenburg syndrome (Shah–Waardenburg syndrome) is the association of Waardenburg syndrome with Hirschsprung disease (congenital aganglionic megacolon).¹⁷¹

Etiology and pathogenesis

Waardenburg syndrome types 1 and 3 are allelic variants and due to mutations in the *PAX3* gene on chromosome 2q.¹⁷² *PAX3* is one of a family of paired box genes that control neural crest differentiation by regulating the transcription of a number of other genes involved in embryological development. The neural crest gives rise not only to melanocytes but also to the bony and cartilaginous structures of the central face, accounting for the dysmorphic features associated with Waardenburg syndrome. Most mutations in *PAX3* result in Waardenburg syndrome type 1. Simple loss of function of one allele will result in the type 1 phenotype due to haploinsufficiency for the *PAX3* gene product

BOX 23.2 TYPES OF WAARDENBURG SYNDROME

TYPE I

1. Autosomal dominant
2. Dystopia canthorum
3. White forelock (poliosis)
4. Piebald skin lesions
5. Synophrys (thickening of medial eyebrows)
6. Broad nasal root
7. Hypoplasia of nasal alae
8. Heterochromia irides
9. Congenital sensorineural hearing loss
10. *PAX3* gene mutations (chromosome 2q36.1)

TYPE II

1. Autosomal dominant
2. Similar features to type I, but lacks dystopia canthorum
3. *MITF* mutations (chromosome 3p12)
4. *SOX10* mutations (chromosome 22q13)

TYPE III (KLEIN-WAARDENBURG)

1. Autosomal dominant
2. Similar features to type I
3. Musculoskeletal abnormalities
4. *PAX3* gene mutations (chromosome 2q36.1)

TYPE IV (SHAH-WAARDENBURG)

1. Autosomal recessive
2. Craniofacial abnormalities
3. No dystopia canthorum
4. Extensive depigmentation
5. Hirschsprung disease
6. Endothelin-3 gene mutations or one of its receptors, endothelin beta receptor (chromosome 13q22.3)
7. *SOX10* mutations



Figure 23.11 Waardenburg syndrome. (Reproduced with permission from Bologna, Jorizzo, Rapini. *Dermatology* 2003; 1:960.)

(heterozygotes). A small fraction of *PAX3* mutations result in the more severe type 3 phenotype, and some of these patients are homozygous for the *PAX3* mutation, suggesting a gene dosage effect.¹⁷³

Waardenburg syndrome type 2 is caused by mutations in the gene encoding the microphthalmia association transcription factor (*MITF*), mapped to chromosome 3p.¹⁷⁴ The *MITF* gene product is a dimeric transcription factor of the basic–helix–loop–helix–leucine zipper class that is expressed in skin, hair follicles, retina and otic vesicles, and is involved in melanocyte differentiation. Type 2 Waardenburg syndrome is a heterogeneous group and some patients are heterozygous for mutations in the *MITF* gene, resulting in haploinsufficiency of the *MITF* protein due to loss of function mutations in one of the alleles of the *MITF* gene.¹⁷⁵ *MITF* is downstream of *PAX3*, and this hierarchy of effect explains the lesser facial abnormalities in Waardenburg syndrome type 2 compared to type 1. Homozygous deletions of the *SNA12* (*SLUG*) gene, encoding snail homolog 2, a zinc-finger transcription factor, have been described in two patients with Waardenburg syndrome type 2.¹⁷⁶ Recently, *SOX10* (*SRY*-sex determining region Y-box 10) mutations have also been reported to account for about 15–30% of cases of Waardenburg syndrome type 2.^{177,178} *SOX10* is located on chromosome 22q13.1 and is a key transcription factor of neural crest development. It is crucial for the survival and maintenance of pluripotency of migrating neural crest progenitors.¹⁷⁹

Waardenburg syndrome type 4 is a rare autosomal recessive condition caused by mutations in the genes for endothelin-3 (*EDN3*), or one of its receptors, endothelin β receptor (*EDNRB*) and to the *SOX10* gene.^{180,181} All of these genes are functionally interrelated and contribute to the formation of the nervous system. *EDNRB* mutations are dosage sensitive: heterozygosity predisposes to isolated Hirschsprung disease, whereas homozygosity results in more complex neurocristopathies associating Hirschsprung disease and Waardenburg syndrome.¹⁸² About 20–30% of cases are due to mutations within the *EDN3* or the *EDNRB* genes and about 45–55% result from mutations within the *SOX10* gene.¹⁸³ Mutations in the *SOX10* gene are also responsible for an extended syndrome called PCWH (peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, Hirschsprung disease), which is caused mostly by mutations in the last coding exon of *SOX10*.¹⁸⁴

Differential diagnosis

Piebaldism should be considered in patients with dominantly inherited patchy depigmentation. The pigmentary disturbances are very similar in both Waardenburg syndrome and piebaldism, but auditory and facial developmental anomalies are absent in piebaldism.¹⁶² Fisch syndrome should be considered in cases of premature graying of the hair and congenital deafness.¹⁸⁵ The association of deafness and vitiligo with an autosomal recessive mode of inheritance is known as Rozycki syndrome.¹⁸⁶

Treatment and care

Physical findings suggestive of Waardenburg syndrome in neonates warrant a hearing evaluation, as detection of the associated deafness allows for early intervention with hearing aids and specialized education. The use of multichannel cochlear implants in Waardenburg syndrome children with profound deafness was found to be useful for the development and

improvement of speech perception and production.¹⁸⁷ Spontaneous pigmentation and contraction of the leukodermic patches in Waardenburg syndrome has been reported.¹⁸⁸ Treatment options for the leukoderma are the same as those for piebaldism.

TUBEROUS SCLEROSIS COMPLEX

Tuberous sclerosis complex (TSC) is an autosomal dominant condition with variable penetrance, characterized by cutaneous and neurologic abnormalities such as mental retardation and seizures as well as visceral hamartomas. Spontaneous mutations account for 66–86% of cases.^{189,190} Estimates of prevalence range from 1:6000 to 1:10000.^{191,192}

Criteria for diagnosis are shown in Box 23.3.¹⁹³

Cutaneous findings

Hypomelanotic macules or patches are the earliest sign of tuberous sclerosis complex and are present in up to 90% of patients.¹⁹⁰ The lesions are almost always present from birth, rarely developing later in infancy or childhood. They have a partial rather than complete loss of pigmentation, and perifollicular pigmentation may be observed in some of them.¹¹⁶ Multiple hypopigmented macules are of concern for TSC, although three or fewer may be a variant of normal and occur in otherwise healthy individuals.¹⁹⁴ Examination under Wood's lamp may be necessary to detect subtle lesions in fair-skinned individuals.¹⁹⁵ The hypopigmented macules can be polygonal (thumbprint), lance-ovate (ash leaf spot) or guttate (confetti-like) (Figs. 23.12, 23.13).¹⁹⁶ Confetti-like lesions appear as

BOX 23.3 DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS COMPLEX

- Definite TSC: either 2 major features or 1 major feature plus 2 minor features
- Probable TSC: one major plus 1 minor feature
- Possible TSC: either 1 major feature or 2 or more minor features

MAJOR FEATURES

1. Facial angiofibromas or forehead plaque
2. Nontraumatic ungual or periungual fibroma
3. Hypomelanotic macules (three or more)
4. Shagreen patch (connective tissue nevus)
5. Multiple retinal nodular hamartomas
6. Cortical tuber
7. Subependymal nodule
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma, single or multiple
10. Lymphangiomyomatosis
11. Renal angiomyolipoma

MINOR FEATURES

1. Multiple randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white matter radial migration lines
5. Gingival fibromas
6. Non-renal hamartoma
7. Retinal achromic patch
8. 'Confetti' skin lesions
9. Multiple renal cysts

(Reprinted from Roach ES, Gomez MR, Northrup H. *J Child Neurol* 1998; 13:624–628.)



Figure 23.12 Tuberous sclerosis. Hypopigmented macules and patches in an infant with cardiac rhabdomyoma.



Figure 23.14 Facial angiofibromas.



Figure 23.13 Tuberous sclerosis. Hypopigmented macule with shagreen patch.



Figure 23.15 Periungual fibromas.

multiple small areas of stippled hypopigmentation, typically on the extremities. Poliosis of scalp hair, eyebrows, or eyelashes may be seen in patients with TSC,¹⁹⁷ as well as circumscribed hypopigmentation of the iris or fundus.¹⁹⁸ Electron microscopy of the hypopigmented macules reveals smaller organelles and a reduction in the size and number of the melanosomes, which exist mainly in the unmelanized stages.¹²⁸

Facial angiofibromas (adenoma sebaceum) are made up of vascular and connective tissue elements and are present in three-quarters of patients representing the most frequent lesion in TSC.¹⁹⁹ They are first noticed between the ages of 2 and 8 years as a few small red papules on the malar area, and gradually become larger and more numerous, sometimes extending down

the nasolabial folds and onto the chin (Fig. 23.14). A fibrous plaque may be seen on the forehead or scalp, is typically present from birth or early infancy, and has a similar histologic appearance to an angiofibroma.¹⁹³ The shagreen patches, which are connective tissue nevi, are found in 20–30% of TSC patients, typically on the back or flank.¹⁹⁰ They appear as slightly raised areas with dimpling at areas of follicular openings, giving the appearance of 'orange peel' or 'gooseflesh'. Ungual and periungual fibromas are nodular or fleshy lesions that arise adjacent to or from underneath the nails (Fig. 23.15). Ungual fibromas usually

occur in adolescents or adults, and are seen in 15–20% of TSC patients.¹⁹⁰ Although they are highly suggestive of TSC, these lesions may occasionally develop spontaneously²⁰⁰ or after trauma. Examination of the mouth can reveal gingival fibromas and small dental enamel pits. Dental pits are more common in older patients with TSC than in unaffected individuals, and particularly affect the permanent teeth.²⁰¹

Extracutaneous findings

These include retinal hamartomas, seen in up to 87% of patients, which appear as classic mulberry lesions adjacent to the optic disc.²⁰² Most retinal lesions are clinically insignificant, although occasional patients may have visual impairment due to a large macular lesion, hamartoma enlargement, retinal detachment, or vitreous hemorrhage.

Up to two-thirds of infants with TSC will have cardiac rhabdomyomas, detected by echocardiography pre- or postnatally.¹⁹⁰ The lesions tend to be multiple, and there is evidence that the majority regress in early childhood.²⁰³ Complications include congestive heart failure, cardiac arrhythmia, or cerebral thromboembolism.²⁰⁴

Renal involvement includes angiomyolipomas, which are benign tumors composed of varying amounts of vascular tissue, fat or smooth muscle, and occur in about two-thirds of TSC patients.²⁰⁵ The prevalence of renal tumors increases throughout childhood, and larger lesions are more likely to become symptomatic than smaller tumors. Single or multiple renal cysts tend to appear earlier than the angiomyolipomas, and the combination of the two is characteristic of tuberous sclerosis complex.¹⁹⁰ The proximity of the *TSC2* gene and the polycystic kidney disease gene may play a synergistic role in cyst development.²⁰⁶ Both angiomyolipomas and renal cysts are often asymptomatic and require no treatment. Hemorrhage is the most common complication of angiomyolipomas, causing hematuria and pain. Renal failure results from obstructive uropathy, or when cysts or tumors replace much of the normal renal parenchyma.

Pulmonary changes are rare, seldom cause symptoms, are five times more common in females, and tend to become clinically manifest in the second decade.²⁰⁷ The most common lesion is pulmonary lymphangiomyomatosis (LAM), which is characterized by a proliferation of abnormal smooth muscle-like LAM cells and leads to pulmonary cysts and pneumothorax.²⁰⁸ Exacerbation during pregnancy and estrogen supplementation has been noted.²⁰⁹ These lesions express estrogen and progesterone receptors, which may explain their gender predilection and sensitivity to hormonal changes. Recurrent spontaneous pneumothorax, dyspnea, cough, hemoptysis, and pulmonary failure are manifestations of pulmonary LAM.

Neurologic manifestations of TSC include mental retardation, seizures, and behavioral problems such as autism,²¹⁰ hyperkinesia, aggressiveness, and psychosis.²¹¹ Infantile spasms are common, occurring in about 70% of affected babies. Neurologic lesions result from impaired cellular interaction, resulting in disrupted neuronal migration along radial glial fibers and abnormal proliferation of glial elements.¹⁹⁰ Neuropathologic lesions include subependymal nodules, cortical hamartomas, focal cortical hypoplasia, and heterotopic gray matter. The number of cortical tubers as observed by magnetic resonance imaging (MRI) has been shown to correlate with the severity of the cerebral dysfunction, with increased numbers of cortical tubers seen in patients with more severe cerebral disease.²¹²

Etiology and pathogenesis

Inactivating mutations in either of two tumor-suppressor genes – *TSC1* and *TSC2* – are the cause of this syndrome, with *TSC2* mutations accounting for 80–90% of all mutations.²¹³ *TSC1* contains 21 coding exons on chromosome 9q34.13 and encodes hamartin of 1164 amino acids; *TSC2* contains 41 exons on 16p13.3, which encodes tuberin of 1807 amino acids.^{214,215} Hamartin and tuberin function as a complex that suppresses a major pathway for the stimulation of cell growth. The hamartin/tuberin complex inactivates GTPase Rheb, which is an activator of the growth-promoting protein kinases rapamycin (mTOR) and P70 S6 kinase (S6K).²¹⁶ *TSC1* and *TSC2* are tumor suppressors that inhibit the mammalian target of rapamycin (mTOR), and if mutated, results in mTOR activation, leading to an increase in protein translation and formation of hamartomas in TSC. Moreover, proto-oncogenes and tumor suppressors, such as *Ras* and *PTEN*, were found to regulate growth via the hamartin/tuberin complex.²¹⁷ Patients with *TSC1* mutations generally have milder disease than patients with *TSC2* mutations, and patients in whom no mutation was found also had milder disease than patients in whom mutations were found.²¹⁸

Differential diagnosis

Lesions that should be distinguished from the hypopigmented macules of TSC include nevus depigmentosus, nevus anemicus, post-inflammatory hypopigmentation, pityriasis alba, tinea versicolor, and vitiligo.¹⁹⁴ Nevus depigmentosus is most easily confused with the hypopigmented macules of TSC.¹¹⁶ A nevus depigmentosus can only be differentiated from a single ash leaf spot by the absence of other signs or symptoms of TSC.

Treatment and care

Management is multidisciplinary. Special education may be required if mental retardation is present. Facial angiofibromas may be treated with the pulsed dye vascular laser. The more nodular lesions may be treated with shave excision and electro-desiccation or with carbon dioxide laser, but slowly recur.²¹⁹

Rapamycin (sirolimus) and the related mTOR inhibitor, everolimus, are immunosuppressive agents traditionally used in transplant recipients. Rapamycin has antineoplastic effects which may be mediated by decreasing the production of vascular endothelial growth factor and it corrects aberrant signaling pathways involved in cell growth and apoptosis.²²⁰ Oral rapamycin at standard immunosuppressive doses has been used as a targeted therapy with promising results for the renal, lung and neurological manifestations of TSC.^{221,222} It can induce regression of visceral angiomyolipomas, brain astrocytomas and improve lung function in patients with lymphangiomyomatosis.

However, regrowth may occur with renal angiomyolipomas after stopping oral rapamycin therapy.²²¹ Topical rapamycin twice daily has been shown to be an effective and safe treatment for facial angiofibromas.^{223–228} Improvement was noted within a week of starting treatment^{223,228} and resolution of lesions in a month to 6 weeks.^{224,227} Topical rapamycin is especially effective in younger children with flatter lesions.²²⁸ Recently, topical rapamycin twice a day for 12 weeks was noted to improve the hypomelanotic macules of TSC.²²⁶ Rapamycin has been shown to increase the transcription of microphthalmia transcription factor (MITF), which is involved in melanogenic gene expression.²²⁹ The main side-effect of topical rapamycin is cutaneous

irritation with undetectable serum rapamycin levels during treatment.^{225,228} Both angiofibromas and hypomelanotic macules may recur a few months after stopping treatment.²²⁶ Rapamycin and its analogues may represent a major advance in therapy.

Examination of the parents and other family members of seemingly sporadic patients with TSC is indicated to exclude the possibility of a mild phenotype of which parents are not aware. Gonadal mosaicism is possible in around 2% of families where parents show no signs of TSC after full clinical evaluation.²³⁰

NEVUS ANEMICUS

Cutaneous findings

Nevus anemicus is a congenital vascular anomaly characterized by single or multiple hypopigmented patches with a normal texture and irregular margins, sometimes surrounded by satellite macules (Fig. 23.16). It appears at birth or in early childhood, and is more common in females.^{231,232} Although it occurs most commonly on the trunk, nevus anemicus has also been reported on the extremities and the head and neck.^{232,233} It persists unchanged throughout life.

Extracutaneous findings

Nevus anemicus may be seen in close association with port wine stains.²³² These twin anomalies may be a result of somatic recombination of allelic mutations for vasoconstriction and vasodilatation.²³⁴ Phakomatosis pigmentovascularis, where vascular and pigmented nevi occur in association with nevus anemicus, has been used to support this concept.²³⁵ Lesions of nevus anemicus occur with increased frequency in patients with neurofibromatosis.²³¹

Etiology and pathogenesis

Examination by light and electron microscopy reveals no abnormality, and the nevus is best characterized as a pharmacological abnormality, rather than an anatomical one.²³³ The pallor is due to an increased local vascular reactivity to catecholamines. Donor dominance was demonstrated by grafting lesional skin from nevus anemicus to normal skin, which retained its pale appearance, emphasizing that nevus anemicus

is due to increased sensitivity of the blood vessels to catecholamines rather than to increased sympathetic stimulation.²³⁶

Differential diagnosis

Under diascopic pressure with a glass microscope slide, the lesion becomes indistinguishable from the blanched surrounding skin.²³⁷ Wood's lamp examination does not accentuate the lesion, and rubbing or temperature change causes erythema in the surrounding area but not within the lesion itself. These maneuvers help to distinguish nevus anemicus from vitiligo, nevus depigmentosus, tuberous sclerosis macules, tinea versicolor, and leprosy.²³⁸ Treatment is cosmetic, and if desired the discoloration can be concealed with camouflage make-up.

VITILIGO

Vitiligo is an acquired disease characterized by well-demarcated depigmented patches caused by destruction of epidermal and follicular melanocytes. Vitiligo affects up to 2% of pediatric populations.²³⁹ It rarely occurs in infancy.

Cutaneous findings

There are several methods of clinical classification. A useful method that provides an indication of the prognosis and treatment is to categorize vitiligo into non-segmental and segmental types.

Segmental vitiligo describes unilateral depigmented patches arranged in a segmental, non-dermatomal pattern (Fig. 23.17). It is seen more commonly in children as compared to adults.²⁴⁰ The face is most commonly affected. It progresses rapidly but tends to be confined within the affected segment and remains stable thereafter.²⁴¹

Non-segmental vitiligo may be generalized, where depigmented patches are distributed symmetrically in more than one region of the body, or localized (focal, acrofacial, acral or mucosal). Children with non-segmental disease are more likely to have more extensive involvement, more frequent progression of disease and thyroid abnormalities on laboratory investigations than children with segmental disease.²⁴²

Extracutaneous findings

Autoimmune diseases like thyroiditis, alopecia areata, diabetes mellitus, pernicious anemia and Addison's disease have been



Figure 23.16 Nevus anemicus.



Figure 23.17 Segmental vitiligo.

reported in children with non-segmental vitiligo. As the frequency of occurrence of these autoimmune diseases is low, thyroid function tests, full blood count and fasting blood glucose can be performed selectively, for example, in a child who fails to thrive.

Etiology and pathogenesis

There is destruction of functional melanocytes by mechanisms that are not fully understood. The autoimmune theory suggests that melanocytes are destroyed by humoral and cell-mediated immunity.²⁴³ Other theories suggest that melanocytes are intrinsically defective, injured by oxidative stress or nerve cells.

Genetic studies provide support for the autoimmune pathogenesis theory in non-segmental vitiligo. *NLRP1* and *XBPI* are vitiligo susceptibility genes that control key aspects of immune regulation. Non-segmental generalized vitiligo has been epidemiologically and genetically associated with some of the other autoimmune diseases, for example, type 1 diabetes mellitus and Addison disease.²⁴⁴

Differential diagnosis

The differential diagnoses of vitiligo include pityriasis alba, tinea versicolor, post-inflammatory hypopigmentation, piebaldism and nevus depigmentosus.²⁴⁵ Pityriasis alba and tinea versicolor, in contrast to vitiligo, are hypopigmented rather than depigmented and often have scaling and indistinct borders. In post-inflammatory hypopigmentation, irregular mottling of both hyperpigmented and hypopigmented areas is often seen. Piebaldism is an autosomal dominant condition presenting at birth with anterior midline depigmentation and a white forelock (poliosis). Nevus depigmentosus is a segmental hypopigmentation detectable at birth or within the first year of life and grows in proportion to the child's growth. With a Wood's lamp, the contrast between lesional and normal skin is less marked than in vitiligo.²⁴⁶

Treatment and care

All children with vitiligo should have photoprotection with a broad-spectrum sunscreen of SPF-30+ during daytime outdoor activity so that sunburn and subsequent koebnerization does not occur.

Cosmetic camouflage such as make-up and self-tanning agents help with the psychosocial burden of vitiligo, especially when extensive and with lesions on exposed skin.²⁴⁷ Self-tanning agents containing dihydroxyacetone (DHA) may be used in older children. It causes the skin to turn brown by polymerizing the amino acids in the skin and is useful to camouflage the depigmented lesions. The desired results usually appear after about 6 h and the resulting pigmentation remains for about 3–4 days.²⁴⁸

In children, mid-potency topical steroids are commonly used as a first-line therapy for localized vitiligo.²⁴⁹ Corticosteroids modulate the immune response by decreasing melanocyte destruction and induces melanocyte repopulation in vitiligo.²⁵⁰ Higher response rates occur in children compared to adults and head and neck lesions respond better.²⁵¹ Complete repigmentation rates have been reported to be as high as 49.3%.²⁵² Frequent monitoring is required to avoid local side effects like atrophy, telangiectasia, striae and steroid folliculitis.

As monotherapy, calcipotriene is inferior to topical corticosteroids, but when combined with topical steroids, repigmentation rates increase with a faster onset of repigmentation along

with greater stability of repigmentation compared with either as monotherapy.²⁵³ Eyelid and facial skin respond best to this combination therapy.²⁵⁴ Off-label use of the fixed stable combined preparation of calcipotriene 0.005%-betamethasone dipropionate 0.064% ointment once daily, is a simple treatment option.²⁵⁵ Calcipotriol has been shown to downregulate the production of IL-8, which is believed to enhance the inflammatory destruction of melanocytes.²⁵⁵

Topical calcineurin inhibitors (TCI), tacrolimus and pimecrolimus, are advantageous in treating vitiligo without the side-effect profile of topical steroids. Tacrolimus inhibits T-cell activation, blocking the production and release of pro-inflammatory cytokines like TNF- α .²⁵⁶ A comparative study revealed 0.1% tacrolimus ointment to be almost as effective as 0.05% clobetasol propionate cream, both used twice a day for the treatment of childhood vitiligo, and tacrolimus may be useful for sensitive areas like the eyelids.²⁵² Repigmentation occurs after 4–6 weeks with 0.1% tacrolimus ointment twice daily and pigmentation is maintained for at least 6–9 months after discontinuation of treatment.²⁵⁷ Pimecrolimus 1% cream twice daily has been shown to be effective in repigmentation of vitiligo in the head and neck region after 6 months of treatment.²⁵⁸ This repigmentation effect of topical pimecrolimus on the face is enhanced by the addition of narrow-band ultraviolet B (NB-UVB) thrice weekly.²⁵⁹ Tacrolimus 0.1% ointment has also been shown to enhance the effect of NB-UVB for the treatment of vitiligo.²⁶⁰

Topical psoralen-ultraviolet A (PUVA) can be used in older children with limited body surface area involvement.²⁶¹ Narrow-band ultraviolet B phototherapy twice or thrice weekly is an effective and safe modality for the treatment of generalized childhood vitiligo with >20% body surface involvement.^{262–265} Better results are seen in children with recent onset disease (<1 year) with best repigmentation over the face and neck and moderate response on the trunk and proximal extremities.²⁶⁴ If no response is seen after 6 months of NB-UVB phototherapy, treatment should be stopped.²⁶⁵ The monochromatic excimer laser (308 nm) allows for the targeted treatment of specific lesions of vitiligo, avoiding the risk of photoaging of the surrounding skin. Cho and colleagues treated 30 children with localized vitiligo with the 308 nm excimer laser and noted a repigmentation rate of 50–75%, especially over the face, neck and trunk.²⁶⁶

Surgical methods may be chosen for older children with stable vitiligo lesions unresponsive to other treatment modalities. Various surgical techniques have been used such as suction blister epidermal grafting²⁶⁷ and autologous non-cultural epidermal cellular grafting. Better results are seen in segmental vitiligo compared to generalized vitiligo.

Whatever treatment is used, certain clinical features are poor prognostic markers for repigmentation. These include acral vitiligo, presence of leukotrichia over the vitiligo, and lesions over bony prominences like the elbows, knees and ankles.²⁴⁹

POST-INFLAMMATORY HYPOPIGMENTATION

Cutaneous findings

Post-inflammatory hypopigmentation refers to the partial loss of melanin in previously inflamed areas of skin. The hypochromic macules and patches usually appear in a mottled pattern in the distribution and configuration of the inflammatory process, and are more obvious in dark skin (Fig. 23.18).



Figure 23.18 Post-inflammatory hypopigmentation secondary to seborrheic dermatitis. Once the inflammation is gone, the hypopigmentation improves.

Etiology and pathogenesis

Post-inflammatory hypopigmentation can appear in the newborn period after inflammatory conditions such as atopic dermatitis, seborrheic dermatitis, diaper dermatitis, psoriasis, pityriasis lichenoides, and infectious conditions.

Differential diagnosis

The differential diagnosis of post-inflammatory hypopigmentation includes pityriasis alba, pityriasis versicolor and vitiligo. Pityriasis alba is characterized by ill-defined, hypopigmented, minimally scaly macules and patches, commonly seen on the face without erythema or pruritus. It is common, being present in 25–40% of dark-skinned children,^{268,269} and occasionally seen in the neonatal period. The histology of post-inflammatory hypopigmentation shows nonspecific findings, such as decreased epidermal melanin, superficial lymphohistiocytic infiltration and presence of melanophages in the upper dermis.²⁷⁰ Wood's lamp will enhance the hypopigmented areas in light skin and helps to distinguish depigmentation from hypopigmentation. Wood's lamp may help to exclude pityriasis versicolor which displays a coppery-orange fluorescence and a potassium hydroxide wet-mount preparation will show the presence of yeast ('spaghetti and meatballs' appearance).

Treatment and care

Treatment of the underlying cause of inflammation will improve the discoloration. Twice-daily application of a mid-strength topical steroid in combination with coal tar has been used to treat post-inflammatory hypopigmentation with some success, although the mechanisms behind this are not well understood.²⁷⁰ Twice-daily application of 1% pimecrolimus cream for 16 weeks has been shown to be beneficial for the treatment of seborrheic dermatitis with associated post-inflammatory hypopigmentation in dark-skinned patients.²⁷¹ Other treatment options for post-inflammatory hypopigmentation include topical psoralen UVA (PUVA), narrowband UVB phototherapy

and the 308 nm excimer laser, which had a response rate of 60–70% after 9 bi-weekly treatments.²⁷² In pityriasis alba, repigmentation is achieved with avoidance of excessive sunlight and topical steroids applied daily for several weeks.

CONGENITAL HALO NEVI

Cutaneous findings

A halo nevus is a benign melanocytic nevus (usually a compound nevus) surrounded by a ring of depigmentation. Depigmented zones around nevi have also been reported with congenital nevi,^{273,274} Spitz nevi, blue nevi, neurofibroma, and primary or metastatic malignant melanoma.²⁷⁵

Halo nevi are often multiple, usually occur on the trunk, and appear most commonly in young people. Vitiligo is often associated and develops at distant sites.²⁷⁴ Children with vitiligo tend to have more multiple halo nevi and a personal and/or family history of autoimmune thyroiditis compared with those with only halo nevi.²⁷⁶ Furthermore, patients with halo nevi and nonsegmental vitiligo tend to have a younger age at onset (<18 years), phototypes I–III, truncal involvement and premature graying of the hair compared to patients with vitiligo alone.²⁷⁷ The condition is usually not inherited, although familial cases have been described.²⁷⁸ The nevus tends to flatten and may eventually involute over a period of months to years, leaving an area of depigmentation that persists for up to a decade or longer, but which eventually may repigment.²⁷⁹

Etiology and pathogenesis

The nevus cells appear to be destroyed by cytotoxic CD8⁺ T-lymphocytes recognizing class I HLA antigens on their surfaces.²⁸⁰ This theory of an immunologic mechanism is supported by the fact that a lymphocytic infiltrate is seen around the nevus cells and the nevus cells show cytotoxic changes.²⁸¹ Unlike acquired halo nevi, congenital halo nevi may have an absence of inflammation on histology and may not involute.^{273,274}

Treatment and care

Usually no treatment is required. Education about the prolonged natural history of halo nevi reassures patients and avoids unnecessary excision.

Miscellaneous hypopigmentation

ALEZZANDRINI SYNDROME

Cutaneous and extracutaneous findings

The syndrome is characterized by unilateral facial vitiligo, ipsilateral tapetoretinal degeneration, poliosis, and perceptive (sensorineural) deafness.^{282,283} Associated insulin-dependent diabetes mellitus and unilateral retinal detachment have been reported,²⁸⁴ as well as bilateral retinal detachment^{283,285} in patients with Alezandrini syndrome.

Symptoms of visual loss begin gradually in one eye between the ages of 12 and 30 years. Vitiligo and poliosis of the scalp ipsilateral to the retinal lesions tend to occur 3–13 years after the visual decline.²⁸⁴ Ipsilateral café-au-lait patches have been reported in combination with the above features.²⁸⁴ Alezandrini syndrome has only been reported in a small number of cases.²⁸⁶

Etiology and pathogenesis

The etiology of Alezzandrini syndrome is unknown. Theories involving viral or autoimmune processes have been postulated.²⁸⁷

Differential diagnosis

A possible variant of this syndrome is the Vogt–Koyanagi–Harada syndrome characterized by vitiligo, poliosis, alopecia areata, chronic uveitis, deafness and meningoencephalitis.

Treatment and care

Medical care includes follow-up fundus examinations, visual acuity tests and audiometry.²⁸⁵ Topical steroids, tacrolimus and use of a sunscreen may be tried on localized areas of vitiligo.

ZIPRKOWSKI–MARGOLIS SYNDROME

Cutaneous and extracutaneous findings

Ziprkowski–Margolis syndrome (albinism–deafness syndrome) is characterized by diffuse hypomelanosis of the skin and hair,

except for the buttocks and genital region.^{288,289} With time, multiple symmetrical macules of hyperpigmentation appear on the trunk and extremities, giving the skin a leopard-like appearance. Other features are heterochromic irides, congenital nerve deafness, and mutism. The syndrome was first reported in a Sephardi Jewish family of Moroccan origin.

Etiology and pathogenesis

The mode of inheritance is X-linked recessive and the *ADFN* gene has been mapped to Xq24–q26.^{290,291} The mutation affects the migration of neural crest-derived precursors of the melanocytes. Female carriers of the diseases can demonstrate sensorineural hearing impairment.²⁹²

Treatment and care

Cochlear implantation for hereditary deafness has been reported to improve the speech perception abilities in patients with the albinism–deafness syndrome.²⁹³

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KEY REFERENCES

8. Toyofuku K, Valencia JC, Kushimoto T, et al. The etiology of oculocutaneous albinism (OCA) type II: the pink protein modulates the processing and transport of tyrosinase. *Pigment Cell Res* 2002;15:217–24.
17. Gahl WA, Brantly M, Kaiser-Kupfer MI, et al. Genetic defects and clinical characteristics of patients with a form of oculocutaneous albinism (Hermansky–Pudlak syndrome). *N Engl J Med* 1998;338:1258–64.
21. Huizing M, Gahl WA. Disorders of vesicles of lysosomal lineage: the Hermansky–Pudlak syndromes. *Curr Mol Med* 2002;2:451–67.
59. Menasche G, Fischer A, de Saint Basile G. Griscelli syndrome types 1 and 2. *Am J Hum Genet* 2002;71:1237–8.
120. Kim SK, Kang HY, Lee ES, et al. Clinical and histopathologic characteristics of nevus depigmentosus. *J Am Acad Dermatol* 2006;55:423–8.
183. Pingault V, Ente D, Dastot-Le Moal F, et al. Review and update of mutations causing Waardenburg syndrome. *Hum Mutat* 2010;31:391–406.
208. Schwartz RA, Fernandez G, Kotulska K, et al. Tuberous sclerosis complex: Advances in diagnosis, genetics and management. *J Am Acad Dermatol* 2007;57:189–202.
228. Foster RS, Bint LJ, Halbert AR, et al. 1% rapamycin for angiofibromas in paediatric patients with tuberous sclerosis: a pilot study of four patients. *Australas J Dermatol* 2012;53:52–6.
244. Spritz RA. Six decades of vitiligo genetics: genome-wide studies provide insights into autoimmune pathogenesis. *J Invest Dermatol* 2012;132:268–73.
252. Lepe V, Moncada B, Castaneda-Cazares JB, et al. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003;139:581–5.

REFERENCES

- King RA, Olds DP. Hairbulb tyrosinase activity in oculocutaneous albinism: Suggestions for pathway control and block location. *Am J Hum Genet* 1985;20:49–55.
- King RA, Oetting WS. Oculocutaneous Albinism. In: Nordlund JJ, Boissy RE, Hearing VJ, et al, editors. *The pigmentary system*. Cambridge, MA: Blackwell; 2006. p. 599–612.
- Tomita Y, Suzuki T. Genetics of pigmentary disorders. *Am J Med Genet* 2004;131C:75–81.
- Bolognia JL. Disorders of hypopigmentation: Update on pathogenesis. *Yale University/Glaxo Dermatology Lectureship Series in Dermatology*, Glaxo; 1997.
- King RA, Summers CG. Albinism. *Dermatol Clin* 1988;6:217–27.
- Orlow SJ. Albinism: An update. *Semin Cutan Med Surg* 1997;16:24–9.
- Ramsay M, Colman MA, Stevens G, et al. The tyrosine-positive oculocutaneous albinism locus maps to chromosome 15q11.2–q12. *Am J Hum Genet* 1992;51:879–84.
- Toyofuku K, Valencia JC, Kushimoto T, et al. The etiology of oculocutaneous albinism (OCA) type II: the pink protein modulates the processing and transport of tyrosinase. *Pigment Cell Res* 2002;15:217–24.
- King RA, Creel D, Cervenka J, et al. Albinism in Nigeria with delineation of new recessive oculocutaneous type. *Clin Genet* 1980;17:259–70.
- King RA, Lewis RA, Townsend D, et al. Brown oculocutaneous albinism: clinical ophthalmological, and biochemical characterization. *Ophthalmology* 1986;92:1496–505.
- Boissy RE, Zhao H, Oetting WS, et al. Mutation in and lack of expression of tyrosinase-related protein-1 (TRP-1) in melanocytes from an individual with brown oculocutaneous albinism: a new subtype of albinism classified as 'OCA3'. *Am J Hum Genet* 1996;58:1145–56.
- Kobayashi T, Urabe K, Winder A, et al. Tyrosinase related protein 1 (TRP1) functions as a DHICA oxidase in melanin biosynthesis. *EMBO J* 1994;13:5818–25.
- Newton JM, Cohen-Barak O, Hagiwara N, et al. Mutations in the human orthologue of the mouse underwhite gene (uw) underlie a new form of oculocutaneous albinism, OCA4. *Am J Hum Genet* 2001;69:981–8.
- Rundshagen U, Zuhlke C, Opitz S, et al. Mutations in the MATP gene in five German patients affected by oculocutaneous albinism type 4. *Hum Mutat* 2004;23:106–10.
- Inagaki K, Suzuki T, Shimizu H, et al. Oculocutaneous albinism type 4 is one of the most common types of albinism in Japan. *Am J Hum Genet* 2004;74:466–71.
- Hermansky F, Pudlak P. Albinism associated with hemorrhagic diathesis and unusual pigmented reticular cells in the bone marrow: report of two cases with histochemical studies. *Blood* 1959;14:162–9.
- Gahl WA, Brantly M, Kaiser-Kupfer MI, et al. Genetic defects and clinical characteristics of patients with a form of oculocutaneous albinism (Hermansky–Pudlak syndrome). *N Engl J Med* 1998;338:1258–64.
- Passeron T, Mantoux F, Ortonne JP. Genetic disorders of pigmentation. *Clin Dermatol* 2005;23:56–67.
- Witkop CJ, Krumwiede M, Sedano H, et al. Reliability of absent platelet dense bodies as a diagnostic criterion for Hermansky–Pudlak syndrome. *Am J Hematol* 1987;26:305–11.
- Shotelersuk V, Dell'Angelica EC, Hartnell L, et al. A new variant of Hermansky–Pudlak syndrome due to mutations in a gene responsible for vesicle formation. *Am J Med* 2000;108:423–7.
- Huizing M, Gahl WA. Disorders of vesicles of lysosomal lineage: the Hermansky–Pudlak syndromes. *Curr Mol Med* 2002;2:451–67.
- Boissy RE, Nordlund JJ. Molecular basis of congenital hypopigmentary disorders in humans: a review. *Pigment Res* 1997;10:12–24.
- Schaffer JV, Paller AS. Genetic disorders of the immune system. In: Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 4th ed. Philadelphia: Mosby Elsevier; 2011.
- Baillieu-Forestier I, Monod-Broca J, Benkerrou M, et al. Generalized periodontitis associated with Chédiak–Higashi syndrome. *J Periodontol* 2008;79:1263–70.
- Misra VP, King RM, Harding AE, et al. Peripheral neuropathy in the Chédiak–Higashi syndrome. *Acta Neuropathol* 1991;81:354–8.
- Blume RS, Wolff SM. The Chédiak–Higashi syndrome: Studies in four patients and review of the literature. *Medicine* 1972;51:247–80.
- Sheramata W, Kott SH, Cyr DP. The Chédiak–Higashi–Steinbrinck Syndrome. *Arch Neurol* 1971;25:289–94.
- Weary PE, Bender AS. Chédiak–Higashi syndrome with severe cutaneous involvement: Occurrence in two brothers 14 and 15 years of age. *Arch Intern Med* 1967;119:381–6.
- Barak Y, Nir E. Chédiak–Higashi syndrome. *Am J Pediatr Hematol Oncol* 1987;9:42–55.
- Pettit RE, Berdal KG. Chédiak–Higashi syndrome. Neurologic appearance. *Arch Neurol* 1984;41:1001–2.
- Rubin CM, Burke BA, McKenna RW, et al. The accelerated phase of Chédiak–Higashi syndrome. An expression of the virus-associated hemophagocytic syndrome? *Cancer* 1985;56:524–30.
- Kinugawa N. Epstein–Barr virus infection in Chédiak–Higashi syndrome mimicking acute lymphocytic leukemia. *Am J Pediatr Hematol Oncol* 1990;12:182–6.
- Tchernev VT, Mansfield TA, Giot L, et al. The Chédiak–Higashi protein interacts with SNARE complex and signal transduction proteins. *Mol Med* 2002;8:56–64.
- Boxer LA, Watanabe AM, Rister M, et al. Correction of leukocyte function in Chédiak–Higashi syndrome by ascorbate. *N Engl J Med* 1976;295:1041–5.
- Weening RS, Schoorel EP, Roos D, et al. Effect of ascorbate on abnormal neutrophil, platelet, and lymphocyte function in a patient with the Chédiak–Higashi syndrome. *Blood* 1981;57:856–65.
- Roder JC, Haliotis T, Klein M, et al. A new immunodeficiency disorder in humans involving NK cells. *Nature* 1980;284:553–5.
- Nair MN, Gray RH, Boxer LA, et al. Deficiency of inducible suppressor cell activity in the Chédiak–Higashi syndrome. *Am J Hematol* 1987;26:56–66.
- Amichai B, Zeharia A, Mimouni M, et al. Picture of the month. *Arch Pediatr Adolesc Med* 1997;151:425–6.
- Brandt EJ, Elliot RW, Swank RT. Defective lysosomal enzyme secretion in kidneys of Chédiak–Higashi (beige) mice. *J Cell Biol* 1975;67:774–88.
- Baetz K, Isaaz S, Griffiths GM. Loss of cytotoxic T lymphocyte function in Chédiak–Higashi syndrome arises from a secretory defect that prevents lytic granule exocytosis. *J Immunol* 1995;154:6122–31.
- Durandy A, Breton-Gorius J, Guy-Grand D, et al. Prenatal diagnosis of syndromes associating albinism and immune deficiencies (Chédiak–Higashi syndrome and variant). *Prenat Diagn* 1993;13:13–20.
- Haddad E, Le Deist F, Blanche S, et al. Treatment of Chédiak–Higashi syndrome by allogeneic bone marrow transplantation: Report of ten cases. *Blood* 1995;85:3328–33.
- Griscelli C, Virelizier JL. Bone marrow transplantation in a patient with Chédiak–Higashi syndrome. *Birth Defects* 1983;19:333–4.
- Tardieu M, Lacroix C, Neven B, et al. Progressive neurologic dysfunctions 20 years after allogeneic bone marrow transplantation for Chédiak–Higashi syndrome. *Blood* 2005;106:40–2.
- Uyama E, Hirano T, Ito K, et al. Adult Chédiak–Higashi syndrome presenting as parkinsonism and dementia. *Acta Neurol Scand* 1994;89:175–83.
- Misra VP, King RHM, Harding AE, et al. Peripheral neuropathy in the Chédiak–Higashi syndrome. *Acta Neuropathol* 1991;81:354–8.
- Courtens W, Broeckx W, Ledoux M, et al. Oculocerebral hypopigmentation syndrome (Cross syndrome) in a gypsy child. *Acta Paediatr Scand* 1989;78:806–10.
- Cross HE, McKusick VA, Breen W. A new oculocerebral syndrome with hypopigmentation. *J Pediatr* 1967;70:398–406.
- Fryns JP, Dereymaeker AM, Heremans G, et al. Oculocerebral syndrome with hypopigmentation (Cross syndrome): Report of two siblings born to consanguineous parents. *Clin Genet* 1988;34:81–4.
- Lidsky AS, Robson KH, Thirumalachary C, et al. The PKU locus in man is on chromosome 12. *Am J Hum Genet* 1984;36:527–33.
- Mineroff AD. Phenylketonuria. In: Nordlund JJ, Boissy RE, Hearing VJ, et al, editors. *The pigmentary system*. 2nd ed. Cambridge, MA: Blackwell; 2006. p. 634–5.
- Scriver CR, Hurtubise M, Konecki D, et al. PAHdb 2003: what a locus-specific knowledge base can do. *Hum Mutat* 2003;21:333–44.
- Scriver CR, Kaufman S. The hyperphenylalaninemias. In: Scriver CR, Beaudet AL, Sly SW, et al, editors. *The metabolic and molecular bases of inherited disease*. 8th ed. New York: McGraw-Hill; 2001.
- Rosenberg LE. Inherited disorders of amino acid metabolism and storage. In: Isselbacher K, Braunwald E, Wilson J, et al, editors. *Harrison's principles of internal medicine*. 13th ed. New York: McGraw-Hill; 1994. p. 2117–25.
- Beasley MG, Costello PM, Smith I. Outcome of treatment in young adults with phenylketonuria detected by routine neonatal screening between 1964 and 1971. *Q J Med* 1994;87:155–60.
- Platt LD, Koch R, Azen C, et al. Maternal phenylketonuria collaborative study, obstetric aspects and outcome: the first six years. *Am J Obstet Gynecol* 1992;166:1150–60.

57. Griscelli C, Durandy A, Guy-Grand D, et al. A syndrome associating partial albinism and immunodeficiency. *Am J Med* 1978;65:691–702.
58. Pastural E, Barrat FJ, Dufourcq-Lagelouse R, et al. Griscelli disease maps to chromosome 15q21 and is associated with mutations in the myosin-Va gene. *Nature Genet* 1997;16:289–92.
59. Menasche G, Fischer A, de Saint Basile G. Griscelli syndrome types 1 and 2. *Am J Hum Genet* 2002;71:1237–8.
60. Menasche G, Pastural E, Feldmann J, et al. Mutations in RAB27A cause Griscelli syndrome associated with haemophagocytic syndrome. *Nature Genet* 2000;25:173–6.
61. Menasche G, Ho CH, Sanal O, et al. Griscelli syndrome restricted to hypopigmentation results from a melanophilin defect (GS3) or a MYO5A F-exon deletion (GS1). *J Clin Invest* 2003;112:450–6.
62. Gomathy S, Duran-McKinster C. Genetic disorders of pigmentation. In: Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 4th ed. Philadelphia: Mosby Elsevier; 2011.
63. Mancini AJ, Chan LS, Paller AS. Partial albinism with immunodeficiency: Griscelli syndrome: Report of a case and review of the literature. *J Am Acad Dermatol* 1998;38:295–300.
64. Haraldsson A, Weemaes CR, Bakkeren JM, et al. Griscelli disease with cerebral involvement. *Eur J Pediatr* 1991;150:419–22.
65. Gogus S, Topcu M, Kucukali T, et al. Griscelli syndrome: Report of three cases. *Pediatr Pathol Lab Med* 1995;15:309–19.
66. Klein C, Philippe N, Le Deist F, et al. Partial albinism with immunodeficiency (Griscelli syndrome). *J Pediatr* 1994;125:886–95.
67. Hurvitz H, Gillis R, Klaus S, et al. A kindred with Griscelli disease: spectrum of neurological involvement. *Eur J Pediatr* 1993;152:402–5.
68. Brismar J, Harfi HA. Partial albinism with immunodeficiency: A rare syndrome with prominent posterior fossa white matter changes. *Am J Neuroradiol* 1992;13:387–93.
69. Bizario JCS, Feldmann J, Castro FA, et al. Griscelli syndrome: characterization of a new mutation and rescue of T-cytotoxic activity by retroviral transfer of RAB27A gene. *J Clin Immunol* 2004;24:397–410.
70. Siccardi AG, Bianchi E, Calligaris A, et al. A new familial defect in neutrophil bactericidal activity. *Helv Paediatr Acta* 1978;33:401–12.
71. Brambilla E, Dechelette E, Stoeber P. Partial albinism and immunodeficiency: Ultrastructural study of haemophagocytosis and bone marrow erythroblasts in one case. *Pathol Res Pract* 1980;167:151–65.
72. Schneider LC, Berman RS, Shea CR, et al. Bone marrow transplantation (BMT) for the syndrome of pigmentary dilution and lymphohistiocytosis (Griscelli's syndrome). *J Clin Immunol* 1990;10:146–53.
73. Rogers SL, Karcher RL, Roland JT, et al. Regulation of melanosome movement in the cell cycle by reversible association with myosin V. *J Cell Biol* 1999;146:1265–76.
74. Bahadoran P, Aberdam E, Mantoux F, et al. Rab27a: A key to melanosome transport in human melanocytes. *J Cell Biol* 2001;152:843–50.
75. Fischer A, Griscelli C, Friedrich W, et al. Bone marrow transplantation for immunodeficiencies and osteoporosis: European survey, 1968–1985. *Lancet* 1986;2:1080–83.
76. Elejalde BR, Holguin J, Valencia A, et al. Mutations affecting pigmentation in man: I. Neuroectodermal melanolyosomal disease. *Am J Med Genet* 1979;3:65–80.
77. Elejalde BR, De Elejalde MM. Neuroectodermal melanolyosomal disease. In: Gomez MR, editor. *Neurocutaneous diseases: A practical approach*. Boston, MA: Butterworth-Heinemann; 1987. p. 254–60.
78. Duran-McKinster C, Rodriguez-Jurado R, Ridaura C, et al. Elejalde syndrome: A melanolyosomal neurocutaneous syndrome: Clinical and morphological findings in 7 patients. *Arch Dermatol* 1999;135:182–6.
79. Ivanovich J, Mallory S, Storer T, et al. 12-year-old male with Elejalde syndrome (neuroectodermal melanolyosomal disease). *Am J Med Genet* 2001;98:313–16.
80. Sanal O, Yel L, Kucukali T, et al. An allelic variant of Griscelli disease: presentation with severe hypotonia, mental-motor retardation, and hypopigmentation consistent with Elejalde syndrome (neuroectodermal melanolyosomal disorder). *J Neurol* 2000;247:570–2.
81. Menasche G, Fischer A, de Saint Basile G. Griscelli syndrome types 1 and 2. *Am J Hum Genet* 2002;71:1237–8.
82. Anikster Y, Huizing M, Anderson PD, et al. Evidence that Griscelli syndrome with neurological involvement is caused by mutations in RAB27A, not MYO5A. *Am J Hum Genet* 2002;71:407–14.
83. Bahadoran P, Ortonne JP, Ballotti R, et al. Comment on Elejalde syndrome and relationship with Griscelli syndrome. *Am J Med Genet* 2003;116A:408–9.
84. Menkes JH, Alter M, Steigleder GK, et al. A sex-linked recessive disorder with retardation of growth, peculiar hair and focal cerebral and cerebellar degeneration. *Pediatrics* 1962;29:764–79.
85. Gu YH, Kodama H, Murata Y, et al. ATP 7A gene mutations in 16 patients with Menkes disease and a patient with occipital horn syndrome. *Am J Med Genet* 2001;99:217–22.
86. Peterson J, Drolet BA, Esterly NB. Menkes' kinky-hair syndrome. *Pediatr Dermatol* 1998;15:137–9.
87. Stratigos AJ, Baden HP. Unraveling the molecular mechanisms of hair and nail genodermatoses. *Arch Dermatol* 2001;137:1465–71.
88. Tumer Z, Moller LB. Menkes disease. *Eur J Hum Genet* 2010;18:511–18.
89. Galve J, Vicente A, Gonzalez-Ensenat MA, et al. Neonatal erythroderma as a first manifestation of Menkes disease. *Pediatrics* 2012;130:e239–42.
90. Hart DB. Menkes' kinky hair syndrome: an updated review. *J Am Acad Dermatol* 1983;9:145–52.
91. Kodama H, Fujisawa C, Bhadrprasit W. Inherited copper transport disorders: biochemical mechanisms, diagnosis, and treatment. *Curr Drug Metab* 2012;13:237–50.
92. Hicks JD, Donsante A, Pierson TM, et al. Increased frequency of congenital heart defects in Menkes disease. *Clin Dysmorphol* 2012;21:59–63.
93. Kodama H, Murata Y, Kobayashi M. Clinical manifestations and treatment of Menkes disease and its variants. *Pediatr Int* 1999;41:423–9.
94. Levinson B, Gitschier J, Vulpe C, et al. Are X-linked cutis laxa and Menkes disease allelic? *Nature Genet* 1993;3:6.
95. Vulpe C, Levinson B, Whitney S, et al. Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATPase. *Nature Genet* 1993;3:7–13.
96. Tumer Z, Moller LB, Horn N. Mutation spectrum of ATP7A, the gene defective in Menkes disease. *Adv Exp Med Biol* 1999;448:83–95.
97. Tsukahara M, Imaizumi K, Kawai S, et al. Occipital horn syndrome: report of a patient and review of the literature. *Clin Genet* 1994;45:32–5.
98. Moller LB, Tumer Z, Lund C, et al. Similar splice-site mutations of the ATP 7A gene lead to different phenotypes: Classical Menkes disease or occipital horn syndrome. *Am J Hum Genet* 2000;66:1211–20.
99. Sarkar B, Lingerat-Walsh K, Clarke JT. Copper-histidine therapy for Menkes disease. *J Pediatr* 1993;123:828–30.
100. Christodoulou J, Danks DM, Sarkar B, et al. Early treatment of Menkes disease with parenteral copper-histidine: Long-term follow-up of four treated patients. *Am J Med Genet* 1998;76:154–64.
101. Borm B, Moller LB, Hausser I, et al. Variable clinical expression of an identical mutation in the ATP 7A gene for Menkes disease/occipital horn syndrome in three affected males in a single family. *J Pediatr* 2004;145:119–21.
102. Sheela SR, Latha M, Liu P, et al. Copper-replacement treatment for symptomatic Menkes disease: ethical considerations. *Clin Genet* 2005;68:278–83.
103. Bologna JL, Orlov SJ, Glick SA. Lines of Blaschko. *J Am Acad Dermatol* 1994;31:157–90.
104. Harre J, Millikan LE. Linear and whorled pigmentation. *Int J Dermatol* 1994;33:529–37.
105. Ito M. Incontinentia pigmenti achromians: A singular case of nevus depigmentosus systematicus bilateralis. *Tohoku J Exp Med* 1952;55:57–9.
106. Torrelo A. Cutaneous mosaicism. In: Schachner LA, Hansen RC, editors. *Pediatric dermatology*. 4th ed. Philadelphia: Mosby Elsevier; 2011.
107. Sybert VP. Hypomelanosis of Ito: A description, not a diagnosis. *J Invest Dermatol* 1994;103:S141–3.
108. Ballmer-Weber BK, Inaebnit D, Brand CU, et al. Sporadic hypomelanosis of Ito with focal hypertrichosis in a 16-month-old girl. *Dermatology* 1996;193:63–4.
109. Loomis CA. Linear hypopigmentation and hyperpigmentation, including mosaicism. *Semin Cutan Med Surg* 1997;16:44–53.
110. Jelinek JE, Bart RS, Schiff SM, et al. Hypomelanosis of Ito ('incontinentia pigmenti achromians'): report of three cases and review of the literature. *Arch Dermatol* 1973;107:596–601.
111. Sybert VP, Pagon RA, Donlan M, et al. Pigmentary abnormalities and mosaicism for chromosomal aberration: association with clinical features similar to hypomelanosis of Ito. *J Pediatr* 1990;116:581–6.
112. Takematsu H, Sato S, Igarashi M, et al. Incontinentia pigmenti achromians (Ito). *Arch Dermatol* 1983;119:391–5.
113. Vormittag W, Ensinger C, Raff M. Cytogenetic and dermatoglyphic findings in a familial case of hypomelanosis of Ito (incontinentia

- pigmenti achromians). *Clin Genet* 1992;41:309–14.
114. Montagna P, Procaccianti G, Galli G, et al. Familial hypomelanosis of Ito. *Eur Neurol* 1991;31:345–7.
 115. Shih IH, Lin JY, Chen CH, et al. A birthmark survey in 500 newborns: clinical observation in two northern Taiwan medical center nurseries. *Chang Gung Med J* 2007;30:220–5.
 116. Pinto FJ, Bologna JL. Disorders of hypopigmentation in children. *Pediatr Clin North Am* 1991;38:991–1017.
 117. Lee HS, Chun YS, Hann SK. Nevus depigmentosus: Clinical features and histopathologic characteristics in 67 patients. *J Am Acad Dermatol* 1999;40:21–6.
 118. Lerner VD. Segmental nevus depigmentosus: Analysis of 20 patients. *Pediatr Dermatol* 1999;16:349–53.
 119. Xu AE, Huang B, Li YW, et al. Clinical, histopathological and ultrastructural characteristics of naevus depigmentosus. *Clin Exp Dermatol* 2008;33:400–5.
 120. Kim SK, Kang HY, Lee ES, et al. Clinical and histopathologic characteristics of nevus depigmentosus. *J Am Acad Dermatol* 2006;55:423–8.
 121. Sugarman GI, Reed WB. Two unusual neurocutaneous disorders with facial cutaneous signs. *Arch Neurol* 1969;21:242–7.
 122. Dawn G, Dhar S, Handa S, et al. Nevus depigmentosus associated with hemihypertrophy of the limbs. *Pediatr Dermatol* 1995;12:286–7.
 123. Dhar S, Kanwar AJ, Kaur S. Nevus depigmentosus in India: experience with 50 patients. *Pediatr Dermatol* 1993;10:299–300.
 124. Nehal KS, PeBenito R, Orlow SJ. Analysis of 54 cases of hypopigmentation and hyperpigmentation along the lines of Blaschko. *Arch Dermatol* 1996;132:1167–70.
 125. Bologna JL, Lazova R, Watsky K. The development of lentigines within segmental achromic nevi. *J Am Acad Dermatol* 1998;39:330–3.
 126. Jagia R, Mendiratt V, Koranne RV, et al. Colocalized nevus depigmentosus and lentigines with underlying breast hypoplasia: a case of reverse mutation? *Dermatol Online J* 2004;10:12.
 127. Taniguchi S, Tsuruta D, Higashi J, et al. Coexistence of generalized milia and naevus depigmentosus. *Br J Dermatol* 1995;132:317–18.
 128. Jimbow K, Fitzpatrick TB, Szabo G, et al. Congenital circumscribed hypomelanosis: A characterization based on electron microscopic study of tuberous sclerosis, nevus depigmentosus and piebaldism. *J Invest Dermatol* 1975;64:50–62.
 129. Lee DJ, Kang HY. Is spontaneous disappearance of nevus depigmentosus possible? *Ann Dermatol* 2012;24:109–11.
 130. Gauthier Y, Surleve-Bazeille JE. Autologous grafting with noncultured melanocytes: A simplified method for treatment of depigmented lesions. *J Am Acad Dermatol* 1992;26:191–4.
 131. Van Geel N, Wallaey E, Goh BK, et al. Long-term results of noncultured epidermal cellular grafting in vitiligo, halo naevi, piebaldism and naevus depigmentosus. *Br J Dermatol* 2010;163:1186–93.
 132. Kim DY, Park YK, Hann SK, et al. *J Am Acad Dermatol* 2008;58:527–9.
 133. Hwang SW, Kang JH, Jung SY, et al. Vitiligo coexistent with nevus depigmentosus: This was treated with narrow-band UVB and these lesions were followed using the Mexameter®, a pigment-measuring device. *Ann Dermatol* 2010;22:482–5.
 134. Kim do Y, Lee KY, Park YK. Use of the 308-nm excimer laser for nevus depigmentosus: a promising treatment for either nevus depigmentosus or vitiligo. *J Dermatol* 2007;34:217–18.
 135. Cooke JV. Familial white skin spotting (piebaldness) ('partial albinism') with white forelock. *J Pediatr* 1952;41:1–12.
 136. Campbell B, Swift S. Partial albinism: nine cases in six generations. *JAMA* 1962;181:1103–6.
 137. Davis BK, Verdol LD. Expansion and contraction of hypomelanotic areas in human piebaldism. *Hum Genet* 1976;34:163–70.
 138. Richards KA, Fukai K, Oiso N, et al. A novel KIT mutation results in piebaldism with progressive depigmentation. *J Am Acad Dermatol* 2001;44:288–92.
 139. Arase N, Wataya-Kaneda M, Oiso N, et al. Repigmentation of leukoderma in a piebald patient associated with a novel c-KIT gene mutation, G592E, of the tyrosine kinase domain. *J Dermatol Sci* 2011;64:147–9.
 140. Sijmons RH, Kristofferson U, Tuerlings JHAM, et al. Piebaldism in a mentally retarded girl with rare deletion of the long arm of chromosome 4. *Pediatr Dermatol* 1993;10:235–9.
 141. Chang T, McGrae JD, Hashimoto K. Ultrastructural study of two patients with both piebaldism and neurofibromatosis 1. *Pediatr Dermatol* 1993;10:224–34.
 142. Tay YK. Neurofibromatosis 1 and piebaldism: A case report. *Dermatology* 1998;197:401–2.
 143. Angelo C, Cianchini G, Grosso MG, et al. Association of piebaldism and neurofibromatosis type 1 in a girl. *Pediatr Dermatol* 2001;18:490–3.
 144. Duarte AF, Mota A, Baudrier T, et al. Piebaldism and neurofibromatosis type 1: family report. *Dermatol Online J* 2010;16:11.
 145. Spritz R. Misdiagnosis of 'neurofibromatosis' in patients with piebaldism. *Dermatol Online J* 2011;17:13.
 146. Stevens CA, Chiang P-W, Messiaen LM. Café-au-lait macules and intertriginous freckling in piebaldism: clinical overlap with neurofibromatosis type 1 and Legius syndrome. *Am J Med Genet Part A* 2012;158A:1195–9.
 147. Giebel LB, Spritz RA. Mutation of the KIT (mast/stem cell growth factor receptor) proto-oncogene in human piebaldism. *Proc Natl Acad Sci USA* 1991;88:8696–9.
 148. Vandenberg GR, DeCastro CM, Taylor H, et al. Cloning and structural analysis of the human c-kit gene. *Oncogene* 1992;7:1259–66.
 149. Spritz RA, Holmes A, Ramesar R, et al. Mutations of the kit (mast/stem cell growth factor receptor) proto-oncogene account for a continuous range of phenotypes in human piebaldism. *Am J Hum Genet* 1992;51:1058–65.
 150. Ward KA, Moss C, Sanders DSA. Human piebaldism: relationship between phenotype and site of kit gene mutation. *Br J Dermatol* 1995;132:929–35.
 151. Perez-Losada J, Sanchez-Martin M, Rodriguez-Garcia A, et al. The zinc-finger transcription factor SLUG contributes to the function of the SCF/c-Kit signaling pathway. *Blood* 2002;100:1274–86.
 152. Sanchez-Martin M, Perez-Losada J, Rodriguez-Garcia A, et al. Deletion of the SLUG (SNA12) gene results in human piebaldism. *Am J Med Genet* 2003;122A:125–32.
 153. Suga Y, Ikejima A, Matsuba S, et al. Medical pearl: DHA application for camouflaging segmental vitiligo and piebald lesions. *J Am Acad Dermatol* 2002;47:436–8.
 154. Spritz RA. Piebaldism, Waardenburg syndrome and related disorders of melanocyte development. *Semin Cutan Med Surg* 1997;16:15–23.
 155. Njoo MD, Nieuweboer-Krobotova L, Westerhof W. Repigmentation of leucodermic defects in piebaldism by dermabrasion and thin split-thickness skin grafting in combination with minigrafting. *Br J Dermatol* 1998;139:829–33.
 156. Guerra L, Primavera G, Raskovic D, et al. Permanent repigmentation of piebaldism by erbium: YAG laser and autologous cultured epidermis. *Br J Dermatol* 2004;150:715–21.
 157. Neves DR, Regis Junior JR, Oliveira PJ, et al. Melanocyte transplant in piebaldism: case report. *An Bras Dermatol* 2010;85:385–8.
 158. Read AP, Newton VE. Waardenburg syndrome. *J Med Genet* 1997;34:656–65.
 159. Waardenburg PJ. A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair with congenital deafness. *Am J Hum Genet* 1951;3:195–253.
 160. Hageman MJ. Waardenburg's syndrome in Kenyan Africans. *Trop Geog Med* 1978;30:45–55.
 161. Nayak CS, Isaacson G. Worldwide distribution of Waardenburg syndrome. *Ann Otol Rhinol Laryngol* 2003;112:817–20.
 162. Dourmishev AL, Dourmishev LA, Schwartz RA, et al. Waardenburg syndrome. *Int J Dermatol* 1999;38:656–63.
 163. Ortonne JP. Piebaldism, Waardenburg's syndrome and related disorders. 'Neural crest depigmentation syndromes'? *Dermatol Clin* 1988;6:205–16.
 164. Orlow SJ. Congenital and genetic disorders associated with hypopigmentation. *Curr Probl Dermatol* 1994;6:157–84.
 165. Winship I, Beighton P. Phenotypic discriminants in the Waardenburg syndrome. *Clin Genet* 1992;41:181–8.
 166. Friedman I, Fisch L. Deafness as part of an hereditary syndrome. *J Laryngol Otol* 1959;73:363–82.
 167. Liu XZ, Newton VE, Read AP. Waardenburg syndrome type II: Phenotypic findings and diagnostic criteria. *Am J Med Genet* 1995;55:95–100.
 168. Giacoia JP, Klein SW. Waardenburg's syndrome with bilateral cleft lip. *Am J Dis Child* 1969;117:344–8.
 169. Kromberg JG, Krause A. Waardenburg syndrome and spina bifida. *Am J Med Genet* 1993;45:536–7.
 170. Klein D. Historical background and evidence for dominant inheritance of the Klein-Waardenburg syndrome. *Am J Med Genet* 1983;14:231–9.
 171. Shah KN, Dalal SJ, Desai MP, et al. White forelock, pigmentary disorder of the irides, and long segment Hirschsprung disease: Possible variant of Waardenburg syndrome. *J Pediatr* 1981;99:432–5.
 172. Hoth CF, Milunsky A, Lipsky N, et al. Mutations in the paired domain of the human PAX-3 gene cause Klein-Waardenburg syndrome (WS-III) as well as Waardenburg syndrome type 1 (WS1). *Am J Hum Genet* 1993;52:455–62.

173. Zlotogora J, Lerer I, Bar-David S, et al. Homozygosity for Waardenburg syndrome. *Am J Hum Genet* 1995;56:1173–8.
174. Tassabehji M, Newton VE, Read AP. Waardenburg syndrome type 2 caused by mutations in the human microphthalmia (MITF) gene. *Nature Genet* 1994;8:251–5.
175. Nobukuni Y, Watanabe A, Takeda K, et al. Analyses of loss-of-function mutations of the MITF gene suggest that haploinsufficiency is a cause of Waardenburg syndrome type 2A. *Am J Hum Genet* 1996;59:76–83.
176. Sanchez-Martin M, Rodriguez-Garcia A, Perez-Losada J, et al. SLUG (SNA12) deletions in patients with Waardenburg disease. *Hum Mol Genet* 2002;11:3231–6.
177. Bondurand N, Dastot-Le Moal F, Stanchina L, et al. Deletions at the SOX10 gene locus cause Waardenburg syndrome types 2 and 4. *Am J Hum Genet* 2007;81:1169–85.
178. Chen HS, Jiang L, Xie ZG, et al. Novel mutations of PAX3, MITF and SOX10 genes in Chinese patients with type 1 or type II Waardenburg syndrome. *Biochem Biophys Res Commun* 2010;397:70–4.
179. Kim J, Lo L, Dormand E, et al. SOX10 maintains multipotency and inhibits neuronal differentiation of neural crest stem cells. *Neuron* 2003;38:17–31.
180. Edery P, Attie T, Amiel J, et al. Mutation of the endothelin-3 gene in the Waardenburg–Hirschsprung disease (Shah–Waardenburg syndrome). *Nature Genet* 1996;12:442–4.
181. Pingault V, Bondurand N, Kuhlbrodt K, et al. SOX 10 mutations in patients with Waardenburg–Hirschsprung disease. *Nature Genet* 1998;18:171–3.
182. Amiel J, Attie T, Jan D, et al. Heterozygous endothelin receptor B (EDNRB) mutations in isolated Hirschsprung disease. *Hum Mol Genet* 1996;5:355–7.
183. Pingault V, Ente D, Dastot-Le Moal F, et al. Review and update of mutations causing Waardenburg syndrome. *Hum Mutat* 2010;31:391–406.
184. Inoue K, Khajavi M, Ohyama T, et al. Molecular mechanism for distinct neurological phenotypes conveyed by allelic truncating mutations. *Nat Genet* 2004;36:361–9.
185. Fisch L. Deafness as part of an hereditary syndrome. *J Laryngol Otol* 1959;73:353–62.
186. Rozycki DL, Reuben RJ, Rapin I, et al. Autosomal recessive deafness associated with short stature, vitiligo, muscle wasting and achalasia. *Arch Otolaryngol* 1971;93:194–7.
187. de Sousa Andrade SM, Monteiro AR, Martins JH, et al. Cochlear implant rehabilitation outcomes in Waardenburg syndrome children. *Int J Pediatr Otorhinolaryngol* 2012;76(9):1375–8.
188. Chang T, Hashimoto K, Bawle EV. Spontaneous contraction of leukodermic patches in Waardenburg syndrome. *J Dermatol* 1993;20:707–11.
189. Fleury P, de Groot WP, Delleman JW, et al. Tuberous sclerosis: The incidence of sporadic cases versus familial cases. *Brain Dev* 1980;2:107–17.
190. Roach ES, Delgado MR. Tuberous sclerosis. *Dermatol Clin* 1995;13:151–61.
191. Osborne JP, Fryer A, Webb D. Epidemiology of tuberous sclerosis. *Ann NY Acad Sci* 1991;615:125–7.
192. Wiederholt WC, Gomez MR, Kurland LT. Incidence and prevalence of tuberous sclerosis in Rochester, Minnesota, 1950 through 1982. *Neurology* 1985;35:600–3.
193. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: Revised clinical diagnostic criteria. *J Child Neurol* 1998;13:624–8.
194. Vanderhooft SL, Francis JS, Pagon RA, et al. Prevalence of hypopigmented macules in a healthy population. *J Pediatr* 1996;129:355–61.
195. Fitzpatrick TB. History and significance of white markers: Earliest visible signs of tuberous sclerosis. *Ann NY Acad Sci* 1991;615:26–35.
196. Dohil MA, Baugh WP, Eichenfield LF. Vascular and pigmented birthmarks. *Pediatr Clin North Am* 2000;47:783–812.
197. McWilliam RC, Stephenson JB. Depigmented hair. The earliest sign of tuberous sclerosis. *Arch Dis Child* 1978;53:961–3.
198. Gutman I, Dunn D, Behrens M, et al. Hypopigmented iris spot. An early sign of tuberous sclerosis. *Ophthalmology* 1982;89:1115–19.
199. Nickel WR, Reed WB. Tuberous sclerosis – special reference to the microscopic alterations in the cutaneous hamartomas. *Arch Dermatol* 1962;85:209–26.
200. Zeller J, Friedmann D, Clerici T, et al. The significance of a single periungual fibroma. Report of seven cases. *Arch Dermatol* 1995;131:1465–6.
201. Sampson JR, Attwood D, al Mughery AS, et al. Pitted enamel hypoplasia in tuberous sclerosis. *Clin Genet* 1992;42:50–2.
202. Kiribuchi K, Uchida Y, Fukuyama Y, et al. High incidence of fundus hamartomas and clinical significance of a fundus score in tuberous sclerosis. *Brain Dev* 1986;8:509–17.
203. Smith HC, Watson GH, Patel RG, et al. Cardiac rhabdomyoma in tuberous sclerosis: their course and diagnostic value. *Arch Dis Child* 1989;64:196–200.
204. Konkol RJ, Walsh EP, Power T, et al. Cerebral embolism resulting from an intracardiac tumor in tuberous sclerosis. *Pediatr Neurol* 1986;2:108–10.
205. van Baal JG, Fleury P, Brummelkamp WH. Tuberous sclerosis and the relation with renal angiomyolipoma. A genetic study on the clinical aspects. *Clin Genet* 1989;35:167–73.
206. Sampson J, Maheshwar M, Aspinwall R, et al. Renal cystic disease in tuberous sclerosis: role of the polycystic kidney disease 1 gene. *Am J Hum Genet* 1997;61:843–51.
207. Dwyer JM, Hickie JB, Garvan J. Pulmonary tuberous sclerosis. Report of three patients and a review of the literature. *Q J Med* 1971;40:115–25.
208. Schwartz RA, Fernandez G, Kotulska K, et al. Tuberous sclerosis complex: Advances in diagnosis, genetics and management. *J Am Acad Dermatol* 2007;57:189–202.
209. Mitchell AL, Parisi MA, Sybert VP. Effects of pregnancy on the renal and pulmonary manifestations in women with tuberous sclerosis complex. *Genet Med* 2003;5:154–60.
210. Smalley SL, Tanguay PE, Smith M, et al. Autism and tuberous sclerosis. *J Autism Dev Dis* 1992;22:339–55.
211. Curatolo P, Cusmai R, Cortesi F, et al. Neuropsychiatric aspects of tuberous sclerosis. *Ann NY Acad Sci* 1991;615:8–16.
212. Goodman M, Lamm SH, Engel A, et al. Cortical tuber count: A biomarker indicating neurologic severity of tuberous sclerosis complex. *J Child Neurol* 1997;12:75–6.
213. Rendtorff ND, Bjerregaard B, Frodin M, et al. Analysis of 65 tuberous sclerosis complex (TSC) patients by TSC2 DGGE, TSC1/TSC2 MLPA, and TSC1 long-range PCR sequencing, and report of 28 novel mutations. *Hum Mutat* 2005;25:374–83.
214. Van Slegtenhorst M, de Hoogt R, Hermans C, et al. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. *Science* 1997;277:805–8.
215. European Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. *Cell* 1993;75:1305–15.
216. Kwiatkowski DJ. Tuberous sclerosis: from tubers to mTOR. *Ann Hum Genet* 2003;67:87–96.
217. Potter CJ, Pedraza LG, Huang H, et al. The tuberous sclerosis complex (TSC) pathway and mechanism of size control. *Biochem Soc Trans* 2003;31:584–6.
218. Dabora SL, Jozwiak S, Franz DN, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. *Am J Hum Genet* 2001;68:64–80.
219. Papadavid E, Markey A, Bellaney G, et al. Carbon dioxide and pulsed dye laser treatment of angiofibromas in 29 patients with tuberous sclerosis. *Br J Dermatol* 2002;147:337–42.
220. Guba M, von Breitenbuch P, Steinbauer M, et al. Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: involvement of vascular endothelial growth factor. *Nat Med* 2002;8:128–35.
221. Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med* 2008;358:140–51.
222. Franz DN, Leonard J, Tudor C, et al. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. *Ann Neurol* 2006;59:490–8.
223. Haemel AK, O'Brian AL, Teng JM. Topical rapamycin. A novel approach to facial angiofibromas in tuberous sclerosis. *Arch Dermatol* 2010;146:715–18.
224. DeKlotz CMC, Ogram AE, Singh S, et al. Dramatic improvement of facial angiofibromas in tuberous sclerosis with topical rapamycin: Optimizing a treatment protocol. *Arch Dermatol* 2011;147:1116–17.
225. Mutizwa MM, Berk DR, Anadkat MJ. Treatment of facial angiofibromas with topical application of oral rapamycin solution (1 mg mL⁻¹) in two patients with tuberous sclerosis. *Br J Dermatol* 2011;165:922–6.
226. Wataya-Kaneda M, Tanaka M, Nakamura A, et al. A novel application of topical rapamycin formulation, an inhibitor of mTOR, for patients with hypomelanotic macules in tuberous sclerosis complex. *Arch Dermatol* 2012;148:138–9.
227. Truchuelo T, Diaz-Ley B, Rios L, et al. Facial angiofibromas treated with topical rapamycin: an excellent choice with fast response. *Dermatol Online J* 2012;18(1):15.
228. Foster RS, Bint LJ, Halbert AR, et al. 1% rapamycin for angiofibromas in paediatric patients with tuberous sclerosis: a pilot study of four patients. *Australas J Dermatol* 2012;53:52–6.
229. Ohguchi K, Banno Y, Nakagawa Y, et al. Negative regulation of melanogenesis by

- phospholipase D, through mTOR/P70 S6 kinase 1 signaling in mouse B16 melanoma cells. *J Cell Physiol* 2005;205:444–51.
230. Verhoef S, Bakker L, Tempelaars AMP, et al. High rate of mosaicism in tuberous sclerosis complex. *Am J Hum Genet* 1999;64:1632–7.
 231. Fleisher TL, Zeligman I. Nevus anemicus. *Arch Dermatol* 1969;100:750–5.
 232. Katugampola GA, Lanigan SW. The clinical spectrum of naevus anaemicus and its association with port wine stains: report of 15 cases and a review of the literature. *Br J Dermatol* 1996;134:292–5.
 233. Greaves MW, Birkett D, Johnson C. Nevus anemicus: a unique catecholamine-dependent nevus. *Arch Dermatol* 1970;102:172–6.
 234. Happle R, Koopman R, Mier PD. Hypothesis: vascular twin naevi and somatic recombination in man. *Lancet* 1990;335:376–8.
 235. Happle R. Allelic somatic mutations may explain vascular twin naevi. *Hum Genet* 1991;86:321–2.
 236. Daniel RH, Hubler WR, Wolf JE, et al. Nevus anemicus. Donor-dominant defect. *Arch Dermatol* 1977;113:53–6.
 237. Mountcastle EA, Diestelmeier MR, Lupton GP. Nevus anemicus. *J Am Acad Dermatol* 1986;14:628–32.
 238. Ahkami RN, Schwartz RA. Nevus anemicus. *Dermatology* 1999;198:327–9.
 239. Krüger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo in children/adolescents and adults. *Int J Dermatol* 2012;51:1206–12.
 240. Cho S, Kang HC, Hahm JH. Characteristics of vitiligo in Korean children. *Pediatr Dermatol* 2000;17:189–93.
 241. Hann SK, Lee HJ. Segmental vitiligo: Clinical findings in 208 patients. *J Am Acad Dermatol* 1996;35:671–4.
 242. Mazereeuw-Hautier J, Bezio S, Mahe E, et al. Segmental and nonsegmental childhood vitiligo has distinct clinical characteristics: a prospective observational study. *J Am Acad Dermatol* 2010;62:945–9.
 243. Le Poole IC, Luiten RM. Autoimmune etiology of generalized vitiligo. *Curr Dir Autoimmun* 2008;10:227–43.
 244. Spritz RA. Six decades of vitiligo genetics: genome-wide studies provide insights into autoimmune pathogenesis. *J Invest Dermatol* 2012;132:268–73.
 245. Alikhan A, Felsten LM, Daly M, et al. Vitiligo: a comprehensive overview. *J Am Acad Dermatol* 2011;65:473–91.
 246. Taieb A, Picardo M. Clinical Practice. Vitiligo. *N Engl J Med* 2009;360:160–9.
 247. Ongenaes K, Dierckxens L, Brochez L, et al. Quality of life and stigmatization profile in a cohort of vitiligo patients and effect of the use of camouflage. *Dermatology* 2005;210:279–85.
 248. Suga Y, Ikejima A, Matsuba S, et al. Medical pearl: DHA application for camouflaging segmental vitiligo and piebald lesions. *J Am Acad Dermatol* 2002;47:436–8.
 249. Palit A, Inamadar AC. Childhood vitiligo. *Indian J Dermatol Venereol Leprol* 2012;78:30–41.
 250. Hann SK, Kim HI, Im S, et al. The change of melanocyte cytotoxicity after systemic steroid treatment in vitiligo patients. *J Dermatol Sci* 1993;6:201–5.
 251. Cockayne SE, Messenger AG, Gawkrödger DJ. Vitiligo treated with topical corticosteroids: children with head and neck involvement respond well. *J Am Acad Dermatol* 2002;46:964–5.
 252. Lepe V, Moncada B, Castaneda-Cazares JB, et al. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003;139:581–5.
 253. Kumaran MS, Kaur I, Kumar B. Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. *J Eur Acad Dermatol Venerol* 2006;20:269–73.
 254. Travis LB, Silverberg NB. Calcipotriene and corticosteroid combination therapy for vitiligo. *Pediatr Dermatol* 2004;21:495–8.
 255. Newman MD, Silverberg NB. Once-daily application of calcipotriene 0.005%+betamethasone dipropionate 0.064% ointment for repigmentation of facial vitiligo. *Cutis* 2011;88:256–9.
 256. Grimes PE, Morris R, Avaniss-Aghajani E, et al. Topical tacrolimus therapy for vitiligo: Therapeutic responses and skin messenger RNA expression of proinflammatory cytokines. *J Am Acad Dermatol* 2004;51:52–61.
 257. Travis LB, Weinberg JM, Silverberg NB. Successful treatment of vitiligo with 0.1% tacrolimus ointment. *Arch Dermatol* 2003;139:571–4.
 258. Boone B, Ongenaes K, Van Geel N, et al. Topical pimecrolimus in the treatment of vitiligo. *Eur J Dermatol* 2007;17:55–61.
 259. Esfandiarpour I, Ekhlas A, Farajzadeh S, et al. The efficacy of pimecrolimus 1% cream plus narrow-band ultraviolet B in the treatment of vitiligo: a double-blind, placebo-controlled clinical trial. *J Dermatolog Treat* 2009;20:14–18.
 260. Nordal EJ, Guleng GE, Rönnevig JR. Treatment of vitiligo with narrowband-UVB (TL01) combined with tacrolimus ointment (0.1%) vs placebo ointment, a randomized right/left double-blind comparative study. *J Eur Acad Dermatol Venerol* 2011;25:1440–3.
 261. Tamesis ME, Morelli JG. Vitiligo treatment in childhood: A state of the art review. *Pediatr Dermatol* 2010;27:437–45.
 262. Njoo MD, Bos JD, Westerhof W. Treatment of generalized vitiligo in children with narrowband (TL-01) UVB radiation therapy. *J Am Acad Dermatol* 2000;42:245–53.
 263. Kanwar AJ, Dogra S. Narrow band UVB for the treatment of generalized vitiligo in children. *Clin Exp Dermatol* 2005;30:332–6.
 264. Brazzelli V, Prestinari F, Castello M, et al. Useful treatment of vitiligo in 10 children with UV-B narrow band (311 nm). *Pediatr Dermatol* 2005;22:257–61.
 265. Percivalle S, Piccinno R, Caccialanza M, et al. Narrowband ultraviolet B phototherapy in childhood vitiligo: evaluation of results in 28 patients. *Pediatr Dermatol* 2012;29:160–5.
 266. Cho S, Zheng Z, Park YK, et al. The 380-nm excimer laser: A promising device for the treatment of childhood vitiligo. *Photodermatol Photoimmunol Photomed* 2011;27:24–9.
 267. Gupta S, Kumar B. Epidermal grafting for vitiligo in adolescents. *Pediatr Dermatol* 2002;19:159–62.
 268. Tay YK, Kong KH, Khoo L, et al. The prevalence and descriptive epidemiology of atopic dermatitis in Singapore school children. *Br J Dermatol* 2002;146:101–6.
 269. Bassaly M, Milae A, Prasad AS. Studies on pityriasis alba. *Arch Dermatol* 1963;88:272–5.
 270. Vachiramon V, Thadanipon K. Postinflammatory hypopigmentation. *Clin Exp Dermatol* 2011;36:708–14.
 271. High WA, Pandya AG. Pilot trial of 1% pimecrolimus cream in the treatment of seborrheic dermatitis in African American adults with associated hypopigmentation. *J Am Acad Dermatol* 2006;54:1083–8.
 272. Alexiades-Armenakas MR, Bernstein LJ, Friedman PM, et al. The safety and efficacy of the 308-nm excimer laser for pigment correction of hypopigmented scars and striae alba. *Arch Dermatol* 2004;140:955–60.
 273. Berger RS, Voorhees JJ. Multiple congenital giant nevocellular nevi with halos: Clinical and electron microscopic study. *Arch Dermatol* 1971;104:515–21.
 274. Brownstein MH, Kazam BB, Hashimoto K. Halo congenital nevus. *Arch Dermatol* 1977;113:1572–5.
 275. Kopf AW, Morrill SD, Silberberg I. Broad spectrum of leukoderma acquisitum centrifugum. *Arch Dermatol* 1965;92:14–35.
 276. Patrizi A, Bentivogli M, Raone B, et al. Association of halo nevus/i and vitiligo in childhood: a retrospective observational study. *J Eur Acad Dermatol Venerol* 2013;27(2):e148–52.
 277. Ezzedine K, Diallo A, Leaute-Labreze C, et al. Halo nevi association in nonsegmental vitiligo affects age at onset and depigmentation pattern. *Arch Dermatol* 2012;148:497–502.
 278. Herd RM, Hunter JA. Familial halo naevi. *Clin Exp Dermatol* 1998;23:68–9.
 279. Aouthmany M, Weinstein M, Zirwas MJ, et al. The natural history of halo nevi: A retrospective case series. *J Am Acad Dermatol* 2012;67:582–6.
 280. Zeff RA, Freitag A, Grin CM, et al. The immune response in halo nevi. *J Am Acad Dermatol* 1997;37:620–4.
 281. Gauthier Y, Surleve-Bazeille JE, Gauthier O, et al. Ultrastructure of halo nevi. *J Cutan Pathol* 1975;2:71–81.
 282. Alezzandrini AA. [Unilateral manifestations of tapeto-retinal degeneration, vitiligo, poliosis, grey hair and hypoacusia]. *Ophthalmologica* 1964;147:409–19.
 283. Cremona AC, Alezzandrini AA, Casala AM. Vitiligo, poliosis and unilateral macular degeneration. *Arch Ophthalmol Buenos Aires* 1961;36:102–6.
 284. Hoffman MD, Dudley C. Suspected Alezzandrini's syndrome in a diabetic patient with unilateral retinal detachment and ipsilateral vitiligo and poliosis. *J Am Acad Dermatol* 1992;26:496–7.
 285. Shamsadini S, Meshkat MR, Mozzafarinia K. Bilateral retinal detachment in Alezzandrini's syndrome. *Int J Dermatol* 1994;33:885–6.
 286. Andrade A, Pithon M. Alezzandrini syndrome: report of a sixth clinical case. *Dermatology* 2011;222:8–9.
 287. Gupta M, Pande D, Lehl SS, et al. Alezzandrini syndrome. *BMJ Case Rep* 2011 Aug 17; doi: 10.1136/bcr.04.2011.4052.
 288. Ziprkowski L, Krakowski A, Adam A, et al. Partial albinism and deaf mutism due to a recessive sex-linked gene. *Arch Dermatol* 1962;86:530–9.
 289. Margolis E. A new hereditary syndrome-sex linked deaf-mutism associated with total albinism. *Acta Genet Stat Med* 1962;12:12–19.

290. Shiloh Y, Litvak G, Ziv Y, et al. Genetic mapping of X-linked albinism-deafness syndrome (ADFN) to Xq26. 3-q27.1. *Am J Hum Genet* 1990;47:20–7.
291. Jacob AN, Kandpal G, Gill N, et al. Toward expression mapping of albinism – deafness syndrome (ADFN) locus on chromosome Xq26. *Somat Cell Mol Genet* 1998;24:135–40.
292. Fried K, Feinmesser M, Tsitsianov J. Hearing impairment in female carriers of the sex-linked syndrome of deafness with albinism. *J Med Genet* 1969;6:132–4.
293. Nishizaki K, Fukushiana K, Oda Y, et al. Cochlear implantation for symptomatic hereditary deafness. *Acta Otolaryngol* 1999; 540(Suppl.):34–7.

Disorders of Hyperpigmentation and Melanocytes

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Introduction

Hyperpigmented lesions, presenting at birth and during the first few weeks of life, are quite common. Pigmented lesions can range from small and isolated to large and multiple. They can exist independently, or in association with other signs and symptoms, and may lead to the diagnosis of a congenital or genetic skin disease. In some cases, hyperpigmented ‘birthmarks’ may not be evident at birth but appear weeks to months later. The relatively light color of infant skin can make some pigmentary disorders difficult to appreciate and thus observation over time may be helpful. Also, over time, melanocytes may produce more pigment and differences between normal and hyperpigmented or hypopigmented skin may become more evident. This chapter serves as an aid for clinicians in diagnosing pigmented lesions in the neonatal and infantile period with an approach based on coloration and localization of lesions with a review of diagnostic criteria, associated conditions, and suggested clinical evaluation when applicable (Table 24.1).

Localized hyperpigmentation – tan-brown

CAFÉ-AU-LAIT MACULES

Café-au-lait macules (CALM) are well-circumscribed, oval to round, hyperpigmented hairless macules or patches that may be noted at birth, during infancy or throughout childhood. CALM may have the color of ‘coffee with milk’ in lighter skinned individuals but in darker skinned persons the color may be more medium to dark brown. The size of CALM ranges from a few millimeters to over 20 cm and can occur anywhere on the body (Fig. 24.1). Morphologically, the borders of CALM have been described as smooth (resembling the ‘coast of California’) to jagged contours (resembling the ‘coast of Maine’), correlating with specific disorders. However, in general, this feature varies widely and it not a reliable diagnostic sign.

The prevalence of CALM varies in the general population with 2.7% of 4641 newborns having one or more macules in a US study.¹ There are great differences in prevalence amongst various racial groups, with an increased number of CALM seen in darker skin types.^{1–4} A higher prevalence (24.2–36%) of CALM has been reported in older children and young adults as compared with infants.^{2,3,5} The presence of up to three CALM has been reported in 10–28% of the general population.^{3,6,7} Multiple CALM, especially six or more, should prompt the clinician to consider underlying disorders (Table 24.2).

Although the diagnosis is generally made through clinical examination, histologic examination of CALM shows increased melanin content in keratinocytes and melanocytes without evidence of melanocyte proliferation. On electron microscopy,

giant melanosomes may be seen. While establishing the diagnosis of CALM, these microscopic features are not useful in determining specific systemic associations (such as neurofibromatosis).

The differential diagnosis of CALM includes a congenital melanocytic nevus, speckled lentiginous nevus, lentigo, Becker’s nevus and forms of pigmentary mosaicism such as nevoid hypermelanosis. Often the distinction will become evident over time. Individual lesions of urticaria pigmentosa or a solitary mastocytoma may also be mistaken for CALM and can be distinguished by the Darier’s sign (the development of urticaria following firm stroking of a mastocytoma) (see Chapter 28).

Treatment of isolated CALM is generally not necessary. Laser therapy, typically with ‘Q-switched’ lasers (Q-switched ruby, Q-switched alexandrite, and Q-switched Nd:YAG), has been attempted for cases considered extensive or disfiguring, but results are inconsistent and repigmentation may occur.^{8–11} CALM may also paradoxically darken with laser treatment and result in postinflammatory hyperpigmentation (usually transient).⁸

Segmental pigmentation disorder (mosaic hyperpigmentation)

Segmental pigmentation disorder (SPD or mosaic hyperpigmentation, pigmentary mosaicism) refers to a hyperpigmented or hypopigmented patch often with a sharp midline demarcation and a less distinct lateral border, commonly located on the trunk.¹² Lesions are often noted in infancy and are described in a segmental block-like pattern resembling a ‘checkerboard’¹³ or following the lines of Blaschko. Those lesions that less commonly involve non-truncal sites (such as the extremity or neck) usually extend onto the torso, and solitary facial involvement has been described. The majority of patients with SPD have no extracutaneous abnormalities. SPD is thought to be due to somatic mutations resulting in cutaneous mosaicism. Extensive cases can be variably associated with chromosomal anomalies. The natural history of SPD has not been reported, but persistence of the hyperpigmentation is expected. A rare biopsy done on a patient with hyperpigmented SPD showed increase melanin in the basal layer, similar to CALM.¹²

SELECTED DISORDERS ASSOCIATED WITH CAFÉ-AU-LAIT MACULES

Neurofibromatosis type 1 (NF-1)

CALM are usually the first presenting sign in NF-1, and multiple CALM can be seen in 90% of patients with NF-1 on the trunk, buttocks and legs.¹⁴ In fair-skinned individuals, CALM may be initially overlooked on cutaneous examination. The number of CALM increases over time during the first decade

TABLE
24.1

Diagnosis using lesion morphology and location

Description of lesions	Location or morphology	Possible diagnoses
Blue-gray/blue-black patches	Torso Face Shoulder/neck Torso, in association with port-wine stain	Mongolian spot Nevus of Ota Nevus of Ito Phakomatosis pigmentovascularis
Labial macules	Perioral More widespread facial Face/trunk Face	Peutz–Jeghers syndrome Carney syndrome LEOPARD syndrome Carney syndrome Centrofocal lentiginosis
Brown sharply defined patches or plaques		Congenital melanocytic nevus Café-au-lait macule
Small brown macules	Perioral/mucosal Widespread, non-mucosal Central face/widespread Involves mucosa Axillary/groin/neck only Central face only, nonmucosal Clustered in a defined body area or segment. Background skin color normal Clustered in a defined body area or segment. Background skin color darker Single	Peutz–Jeghers syndrome LEOPARD syndrome Generalized lentiginosis Inherited patterned lentiginosis Carney syndrome Neurofibromatosis Centrofocal lentiginosis Segmental lentiginosis Mosaicism Speckled lentiginous nevus Congenital melanocytic nevus
Linear hyperpigmentation in Blaschko pattern	Flat Raised	Linear and whorled nevoid hypermelanosis (early) Epidermal nevus Incontinentia pigmenti (stage 3) Goltz syndrome Conradi–Hünemann syndrome Mosaicism Human chimerism Epidermal nevus Incontinentia pigmenti (stage 1, 2)



Figure 24.1 A child with NF-1 and numerous and variously sized café au lait macules over the trunk.

of life and lesions tend to grow in proportion to the child and may darken with sun exposure. Axillary and/or inguinal freckling is usually absent at birth but present by age 3–5 years, although it may be noted earlier.¹⁵ This common feature tends to be the cutaneous sign, along with multiple CALM, that establishes the diagnosis and is felt to be pathognomonic for NF-1.¹⁶ Multiple CALM can be seen in other variants of NF, including neurofibromatosis type 2, segmental NF-1 and hereditary spinal neurofibromatosis. A more extensive discussion of NF can be found in [Chapter 29](#).

Legius syndrome

Legius syndrome (neurofibromatosis type 1-like syndrome) is a recently identified autosomal dominant disorder caused by a mutation in the *SPRED1* gene.¹⁷ The *SPRED1* gene is responsible for making spread-1 protein which inhibits the Ras/MAPK pathway. Affected individuals typically have CALM and axillary freckling. However, neurofibromas, typical osseous lesions, Lisch nodules of the iris and central nervous system tumors are characteristically absent. Some patients with Legius syndrome have been described with macrocephaly, a Noonan-like facial appearance, learning disorders, developmental delay and/or attention deficit/hyperactivity disorder in childhood.^{17,18} Several families with Legius syndrome have been described with lipomas as well.^{17–19} Many individuals may meet the NIH diagnostic criteria for NF-1 but gene testing will be negative for mutations in the neurofibromin gene. It is uncertain if there is

TABLE
24.2

Disorders associated with multiple café-au-lait macules (CALM) and associated features

Strong association		Weaker association ^b	
	Major features		Major features
Familial inherited CALM ^a	Multiple (≥ 2) generations with multiple (≥ 10) CALM and other NF-1 stigmata (–)	Tuberous sclerosis	Hypopigmented macules, facial angiofibromas, CNS tubers, retinal hamartomas, renal cysts, angiomyolipoma, cutaneous collagenomas, seizures, mental retardation, cardiac rhabdomyoma, periungual fibromas, subependymal giant cell astrocytomas
Neurofibromatosis type I	Skin-fold freckling, neurofibromas, Lisch nodules, neurocognitive deficits, optic glioma, skeletal dysplasia, macrocephaly	Bloom syndrome	Short stature, photosensitivity, susceptibility to malignancy, chronic lung disease, immunodeficiency, cryptorchidism
Neurofibromatosis type II	Acoustic neuromas, meningiomas, cataracts, schwannomas, neurofibromas	Ataxia-telangiectasia syndrome	Progressive cerebellar ataxia, lymphoreticular malignancy, cutaneous/ocular telangiectasia, immunodeficiency, hypogonadism
Legius syndrome	Macrocephaly, skin-fold freckling, developmental disorders	Silver–Russell syndrome	Congenital short stature and low birthweight, craniofacial and body asymmetry, limb anomalies, microcephaly
Watson syndrome	Short stature, pulmonary stenosis, low intelligence, skin-fold freckling	Bannayan–Riley–Ruvalcaba syndrome	Congenital macrosomia, megalencephaly, lipomas, intestinal polyps, vascular anomalies
Ring chromosome syndrome	Microcephaly, mental retardation, short stature, skeletal anomalies	Noonan syndrome	Facial dysmorphism, pulmonic valve stenosis, webbed neck, pectus excavatum, mental retardation, short stature, cryptorchidism, hematologic malignancies
Hereditary spinal neurofibromatosis	Skin-fold freckling, spinal root neurofibromas	Faconi anemia	Bone marrow failure, limb anomalies, mental retardation, microcephaly, predisposition to malignancy
McCune–Albright syndrome	Polyostotic fibrous dysplasia, endocrinopathies	Turner syndrome	Short stature, lymphedema, congenital heart disease, valgus deformity
		LEOPARD syndrome (multiple lentiginos syndrome)	Multiple lentiginos, hypertelorism, pulmonic valve stenosis, EKG abnormalities, sensorineural deafness, growth retardation, genitourinary abnormalities
		Multiple endocrine neoplasia syndrome type I	Parathyroid adenoma, pituitary adenoma, pancreatic islet adenoma, lipomas, gingival papules, facial angiofibromas, collagenomas

^aArnsmeier, Riccardi and Paller²⁰ proposed that absence of two consecutive generations of neurofibromas and other non-pigmentary changes of NF-1 allows the diagnosis of familial CALM.

^bSyndromes listed have been described with CALM but these are not considered part of the diagnostic criteria, and may not be seen in all cases.

an increased risk of malignancies. However, some authors have proposed less stringent monitoring in Legius patients as compared to NF-1 patients.¹⁸ Screening for developmental delay and behavioral and learning problems is recommended as well as examination and counseling by a clinical geneticist familiar with Legius syndrome.

Familial (inherited) café-au-lait macules

Multiple familial CALM have been described in several families without the other stigmata of NF-1, including the absence of NF-1 gene mutation. *SPRED1* had not been tested in these families.²⁰ This diagnosis should only be made in an older child without the other stigmata of NF-1 with a clear family history of multiple CALM without other signs of NF-1.⁴

McCune–Albright syndrome

The cardinal features of McCune–Albright syndrome (MAS) include polyostotic fibrous dysplasia, endocrinopathies and precocious puberty as well as CALM. MAS is a rare and sporadic disorder caused by a postzygotic mutation in the gene, *GNAS1*.^{21–23} The *GNAS1* gene encodes for the alpha subunit of the guanine nucleotide-binding protein, causing loss of GTPase

activity and increased stimulation of the adenylate cyclase system, resulting in proliferation and autonomous hyperfunction of hormonally responsive cells.^{24–26} This autosomal dominant mutation is only compatible with life when it occurs in individuals as a postzygotic somatic mutation with resulting mosaicism, which in turn results in marked phenotypic variability.

The CALM seen in MAS are often large, and segmental with favored distribution over the torso and buttocks. They may also follow the lines of Blaschko (Fig. 24.2).^{27,28} The border of the CALM in MAS is often described as ‘jagged’ and irregular. These cutaneous findings may be present at birth or within the first few years of life and have been noted in approximately 53–98% of patients with MAS.^{29,30} Melanotic macules of the oral mucosa have also been reported.^{31,32}

Extracutaneous findings in MAS include polyostotic fibrous dysplasia, where bone is replaced by fibrous tissue resulting in asymmetry, bony growths and pathologic fractures; this finding is rarely seen at birth and tends to manifest over time, usually within the first decade. In addition, endocrine abnormalities that may occur include precocious puberty, hyperthyroidism, Cushing syndrome, hyperparathyroidism, hyperprolactinemia,



Figure 24.2 Café-au-lait macules in Blaschkoid distribution in a neonate with McCune–Albright syndrome.

and hypersomatotropism.^{25,33–35} Neonatal cholestasis, acholic stools and jaundice have been described as presenting symptoms in neonates with MAS.³⁵

Due to the variable clinical expression and segmental nature, diagnosis of MAS may be difficult in infancy. Cutaneous findings of MAS must be differentiated from NF-1. The CALM found in NF-1 tend to be smaller, lighter in color, and more scattered in distribution. Histologic studies would not be helpful in differentiating these disorders. Radiologic studies for MAS may not reveal bony abnormalities in the neonatal period and CALM often precede the development of bony changes by 3 months to 9 years.³⁶ When MAS is suspected, close observation for endocrine abnormalities is warranted. In those with known or suspected MAS, a referral to orthopedics and endocrinology is recommended. Prognosis for MAS is generally favorable and the development of malignancy is rare. Extensive osseous dysplasia early in life, however, portends a poorer prognosis.³⁶

DISORDERS OF DERMAL MELANOCYTOSIS

The presence of dermal melanocytes in the skin can give rise to several clinically appearing blue-gray, green or black lesions on the skin including congenital dermal melanocytosis (Mongolian spots), Nevus of Ota, Nevus of Ito and blue nevi. The blue color is due to the Tyndall effect: the scatter of light passing through a turbid medium, such as the dermis, as it strikes melanin particles.

Congenital dermal melanocytosis (Mongolian spots)

Mongolian spots are common birthmarks present in over 80% of black and Asian infants compared with only up to 10% of Caucasians infants.^{37,38} They present at birth, or early infancy, as blue-gray, blue-green, or blue-black macules most often noted over the sacrum and gluteal regions (Fig. 24.3) and less often on extensor extremities and the posterior shoulder. Size can range from a few millimeters to over 10 cm and single or multiple lesions may be present. The borders of Mongolian spots are ill-defined and tend to fade gradually into the surrounding skin color. The coloration will often stabilize in infancy and fade during the first decade of life. Only a small number of lesions persist (3–4%) after adolescence and it has been suggested that these are likely not distinct entities but analogous to Nevus of Ota or Ito.^{37,39–41} Clinically, these persistent lesions are often blue-black homogenous or speckled patches present in a segmental distribution.



Figure 24.3 Mongolian spot on the buttocks.

In the Mongolian spot, elongated, slender and slightly wavy dendritic cells containing melanin granules are found in the mid and deep dermis.⁴² These dendritic melanocytes are present in low numbers and scattered between collagen bundles, both of which are orientated parallel to the skin surface. There is an absence of melanophages. The reason for regression of Mongolian spots and failure of regression of other dermal melanocytic lesions such as nevus of Ito or Ota with age is currently unknown.

Mongolian spots are common, and associated abnormalities are rare. Dermal melanocytosis may be associated with certain lysosomal storage diseases, including gangliosidosis type 1 (GM1), Niemann–Pick disease, Hunter syndrome, α -mannosidosis syndrome, and Hurler syndrome.⁴³ Dermal melanocytosis is generally extensive in distribution often involving the ventral and dorsal aspects of the trunk in addition to the sacrum and extremities.^{44–50} Mongolian spots may also co-exist within CALM in NF-1.^{51,52} Dermal melanocytosis is part of the criteria for a subgroup of neurocristopathies labeled ‘phakomatosis pigmentovascularis’ (PPV), in which vascular malformations of the skin, pigmented nevi and Mongolian spots occur together in the same patient (see below). Cleft lip malformation has been associated with adjacent dermal melanocytosis although the significance of the association is unknown.^{53,54}

Treatment and care. Typical Mongolian spots will fade over time and treatment is usually not needed. For those lesions that persist, laser therapy has been reported to cause lightening with variable success.^{55–57}

Differential diagnosis. Mongolian spots are clinically diagnosed by their common location, congenital or neonatal onset, and morphology, and a biopsy is most often not needed. Other blue lesions include Nevus of Ito, Nevus of Ota, and congenital blue nevus. Location and persistence over time will help in differentiating these entities. A biopsy can be helpful in verifying the dermal location of melanocytes if the diagnosis is in question.

Nevus of Ota (nevus fuscoceruleus ophthalmomaxillaris, oculodermal melanocytosis)

Bluish hyperpigmentation of the skin along the ophthalmic and maxillary branches of the trigeminal nerve is known as Nevus of Ota (Fig. 24.4). These patches can be brown, blue-gray or blue-black, gray or purple and have a speckled or mottled appearance with poorly-demarcated borders. Nodular areas



Figure 24.4 Nevus of Ota involving the forehead, cheek and sclera.

similar to blue nevi can be present.^{58–61} Nevus of Ota often affects one side of the face and bilateral involvement is described in only 5–10% of patients.^{62,58,63} Distribution of Nevus of Ota most commonly involves the ophthalmic and maxillary branches with involvement of all three branches of the trigeminal nerve being the least common distribution.^{41,60,63} This condition is more commonly seen in Asians and has a female preponderance. They may be present at birth or appear within the first year of life, or later between the ages of 11–20 years; mid-childhood onset is rare. Spontaneous resolution does not occur as seen in Mongolian spots. Pathology of cutaneous lesions shows a greater concentration of elongated, dendritic dermal melanocytes scattered within the collagen bundles in the upper dermis (compared with Mongolian spots).

In addition to cutaneous involvement, Nevus of Ota involving the ocular sclera can be seen in two-thirds of patients.⁶⁴ Pigmentation of the sclera, conjunctiva, cornea, iris and choroid, and less commonly, the optic nerve, retrobulbar fat, orbital periosteum and extraocular muscles can occur. Oral mucosal pigmentation and pigmentation of the tympanic membrane can occur as well.

Most Nevi of Ota pose a potential cosmetic concern but few may be associated with complications. Open-angle glaucoma occurs in approximately 10% of patients due to proliferation of melanocytes in the anterior chamber angle.^{65,66} The most concerning complication is the development of melanoma within pigmented areas. Malignant degeneration has been reported and may include the eye (choroid, iris, or orbit), skin, and brain.^{67–69} Sturge–Weber syndrome, Klippel–Trenaunay syndrome, neurofibromatosis, inflammatory vascular disease, cerebral arteriovenous malformation, multiple hemangiomas, and spinocerebellar degeneration have been described occurring in association with Nevus of Ota.^{70–75} Rare occurrences of ipsilateral hearing loss with Nevus of Ota have been reported.^{76,77} Nevus of Ota occurring with nevus flammeus is seen in variants of phakomatosis pigmentovascularis. Leptomenigeal melanosis and Nevus of Ota can occur concurrently as well.^{68,69,75,78,79}



Figure 24.5 Nevus of Ito.

Treatment and care. Nevus of Ota tends to increase in size and color intensity over time. An ophthalmologic examination is recommended for those with involvement of periorbital skin, and yearly examinations for those with ocular pigmentation. Dermatologic follow-up is recommended periodically and removal of stable lesions for melanoma prophylaxis is unnecessary since the risk is quite low.⁵⁸ Opaque make-up may be an option as a means of providing cosmetic improvement. Laser surgery with Q-switched devices (ruby, Nd:YAG or alexandrite) has been shown to reduce the coloration safely and remains the treatment of choice.^{80–84}

Differential diagnosis. The differential diagnosis of Nevus of Ota in a neonate includes a CALM, speckled lentiginous nevus, congenital blue nevus and ochronosis.

Nevus of Ito (nevus fuscoceruleus acromiodeltoideus)

The Nevus of Ito is an analogous lesion to Nevus of Ota with a distribution over the posterior supraclavicular and lateral cutaneous branch of the axillary nerve. These blue-gray poorly-demarcated patches may present over the shoulder, supraclavicular neck, upper arm, scapular and deltoid areas (Fig. 24.5). Bilateral nevus of Ito has been reported in a patient with a speckled lentiginous nevus,⁸⁵ and bilateral Nevus of Ota with a unilateral Nevus of Ito has been noted.⁸⁶ Cutaneous melanoma and malignant cellular blue nevus have been rarely reported in Nevus of Ito and extracutaneous findings are not seen.^{87–89}

Blue nevi

Blue nevi are dermal melanocytomas that represent benign proliferations of pigment producing dendritic dermal melanocytes (Fig. 24.6). Dermoscopy of common blue nevi reveals uniform blue coloration. Blue nevi are rarely seen at birth, but congenital forms have been described.^{90–92} Most are acquired, with onset in childhood or adolescence, with predilection for the scalp and face, dorsal aspects of the distal extremities and sacral area. Three types of blue nevi have been described: (1) cellular blue nevus, (2) common blue nevus, and (3) the combined nevus.

Cellular blue nevi seen at birth are rare and have a predilection for the scalp, sacrococcygeal area and buttocks. They present with blue-gray or blue-black nodules or plaques with a smooth or irregular surface texture. Although most congenital

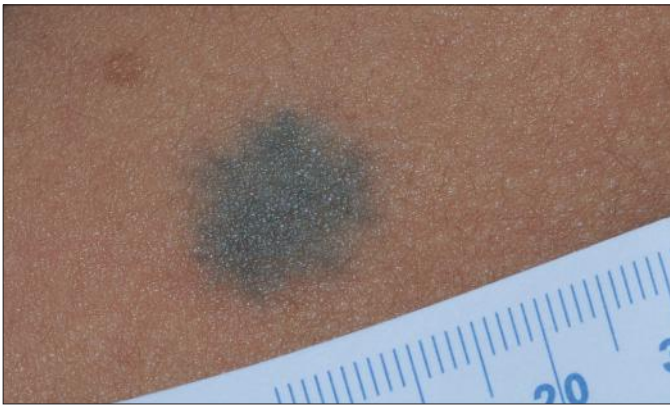


Figure 24.6 Typical-appearing blue nevus.

cellular blue nevi are small in size (1–3 cm), larger and ‘giant’ lesions can be seen, most commonly on the scalp.⁹³ Melanoma has been described particularly in larger lesions on the scalp.^{92–104} Multiple satellite blue nevi in association with a large congenital cellular blue nevus have also been reported.^{93,105} Other related variants of congenital blue nevi include the paucimelanotic cellular blue nevi, epithelioid blue nevi (also known as pigmented epithelioid melanocytoma), congenital plaque-type blue nevi and neurocristic hamartomas. Multiple blue nevi may be seen in Carney complex (see below) or without associated abnormalities. A rare, congenital, plaque-like type of blue nevus, showing a circumscribed area with numerous macules and papules has been described.¹⁰⁶ Blue nevi may arise within speckled lentiginous nevi as well as within other dermal melanocytoses such as Nevus of Ota.^{58,107,108}

Blue-black nodules, papules and plaques seen at birth or infancy are suggestive of blue nevi. A biopsy may be needed to confirm the diagnosis and differentiate lesions from melanoma. Common blue nevi will show pigmented dendritic melanocytes singly or in small aggregations in the reticular dermis, surrounded by thickened collagen. Histopathology of cellular blue nevi, in contrast, shows cellular islands of large spindle-shaped or epithelioid cells with little or no melanin, in addition to pigmented dermal dendritic melanocytes. Lesions may penetrate deep into the subcutaneous fat.⁴²

Treatment and care. Infants with blue nevi that are not easy to monitor due to location and color, as well as those undergoing rapid growth or symptoms (ulceration, bleeding), should be considered for prophylactic surgical excision. Clinically stable, small common blue nevi without unusual or atypical clinical or dermoscopic features may be monitored. Although malignant blue nevi are rare, new atypical features or symptoms should be evaluated histologically via biopsy or conservative excision.

MOSAIC CONDITIONS AND PATTERNED DYSPIGMENTATION (WHORLED AND SEGMENTAL HYPERPIGMENTATION)

Mosaic conditions

Mosaicism is the presence of two or more genetically distinct cell lines in a single individual, which may arise from a variety of genetic defects from separate single mutations, groups of mutations or chromosomal differences.¹⁰⁹ Cutaneous mosaicism

BOX 24.1 CONDITIONS WITH HYPERPIGMENTATION ALONG LINES OF BLASCHKO

- Early (macular) epidermal nevus
- Incontinentia pigmenti
- Linear and whorled nevoid hypermelanosis
- Human chimerism
- Chromosomal mosaicism
- Naegeli–Franceschetti–Jadassohn syndrome
- X-linked cutaneous amyloidosis (female carriers)
- Focal dermal hyperplasia
- Conradi–Hünemann disease, X-linked variant

is associated with diverse pigmentary patterns along the lines of Blaschko or in segmental or block-like patterns, such as the pigmentary anomalies found with hypomelanosis of Ito and McCune–Albright syndrome.^{27,110–112} Many hyperpigmented conditions present in segmental or Blaschko-linear patterns and may be isolated skin findings or coincide with systemic manifestations (Box 24.1).^{113,114}

Chimerism

A chimera refers to an individual with cells derived from two separate zygotes that can be demonstrated by molecular analysis. Human chimerism is rare. Nevoid hyperpigmentation patterns described in human chimeras have included a flag-like rectangular pattern, a pattern of rounded units (café-au-lait-like patches) and a striated pattern.¹¹⁵

Linear and whorled nevoid hypermelanosis

The term ‘linear and whorled nevoid hypermelanosis’ (LWNH) is generally used to describe a sporadic disorder of hyperpigmentation in swirls and streaks following a Blaschkoid distribution. Classically, the hyperpigmentation consists of homogenous 1–5 mm macules forming a reticulated configuration and sparing the palms, soles, mucous membranes and eyes.¹¹⁶ Segmental, linear or swirled hyperpigmentation or a combination of these with a sharp midline demarcation is seen over the trunk and less commonly involving the extremities (Fig. 24.7).¹¹⁷ LWNH appears at birth or during the first few weeks to months of life without any preceding inflammatory eruption. The pigmentation may progress for the first 1–2 years of life and then stabilize, possibly becoming less prominent over time. Biopsy of the hyperpigmented macules shows basilar hyperpigmentation with no pigment incontinence or dermal melanophages.¹¹⁶

Systemic abnormalities seen in association with LWNH include neurologic, developmental, musculoskeletal, and cardiac abnormalities that often arise early in life;^{117–119} LWNH has been described as akin to hypomelanosis of Ito (HI) with cutaneous hyperpigmentation instead of hypopigmentation. No large study exists to define the incidence of systemic features in patients with LWNH. However, systemic comorbidities are described much less frequently in association with LWNH as compared with HI.^{119,117}

LWNH is believed to result from somatic mosaicism of neuroectodermal cells deriving from neural crest, with normal and hyperpigmented skin a result of two distinct populations of cells.^{116,120} Chromosomal mosaicism has also been described.^{114,121–126} Although thought to be a sporadic disorder, rare familial occurrences of LWNH have been reported, suggesting an undescribed gene abnormality.¹²⁷



Figure 24.7 Localized, whorled hyperpigmentation, considered a sign of cutaneous mosaicism. This child was clinically well.

LWNH is usually diagnosed clinically and should be distinguished from other conditions with Blaschkoid hyperpigmentation (Box 24.1). With diffuse skin disease, it can be difficult to deem which coloration represents the patient's normal skin and whether the affected areas are represented by hyper- or hypopigmentation. Skin biopsy will enable differentiation from some conditions such as incontinentia pigmenti (IP) and early (macular) epidermal nevus.

Treatment and care. No specific treatment for LWNH has been described. Thorough history and physical examination should be undertaken to exclude underlying systemic associations. If other anomalies exist, blood and skin fibroblast chromosomal analysis should be considered to look for chromosomal abnormalities.

Incontinentia pigmenti

Incontinentia pigmenti (IP; see also Chapter 29) is an X-linked dominant hereditary disorder found predominantly in females, manifesting with characteristic skin findings, various tooth, eye and nail abnormalities, and neurologic and immunologic impairment. Incontinentia pigmenti is due to a mutation in the *IKK-gamma* (NEMO) gene.¹²⁸

The cutaneous findings of the IP syndrome are evident at birth or shortly thereafter and have been classically defined by four stages: (1) vesiculobullous, (2) verrucous, (3) hyperpigmented and (4) hypopigmented.¹²⁹ However, all four stages may not be seen over time, or they may overlap throughout life. The first inflammatory vesiculobullous stage presents with streaks of eosinophil-filled epidermal vesicles in a geometric fashion, mainly on the extremities, followed by verrucous or lichenoid lesions, and papules and pustules within 2–6 weeks (Fig. 24.8). This stage may persist for several months. Once resolved, widely disseminated hyperpigmentation in a whirled or linear fashion arises, mainly on the trunk. The third stage generally resolves over years and may completely disappear. A fourth stage of atrophy and hypopigmentation, commonly over the lower extremities, may replace the hyperpigmented areas. This stage may be subtle and faint and can be easily overlooked in adult females.¹³⁰

The differential diagnosis of the hyperpigmented stage of IP includes linear and whorled nevoid hypermelanosis,



Figure 24.8 Overlapping hyperpigmented and verrucous stages of incontinentia pigmenti in a newborn.



Figure 24.9 Phakomatosis pigmentovascularis type II. Extensive dermal melanocytosis (Mongolian spot) and port wine stain.

macular epidermal nevi and other disorders with Blaschkoid pigmentation.

Phakomatosis pigmentovascularis

Phakomatosis pigmentovascularis (PPV) is defined by the presence of a widespread vascular malformation, in particular a capillary malformation (port-wine stain), with cutaneous pigmented lesions such as dermal melanocytosis (usually slate-gray or blue melanosis or Mongolian spot-like) or nevus spilus with various other cutaneous nevi (nevus anemicus, epidermal nevus, cutis marmorata telangiectatica) and possible extracutaneous alterations. Pigmentation in PPV is often diffuse (>50% of the skin) and persistent and does not correlate with the typical locations for Mongolian spots (Fig. 24.9).¹³¹

A classification system based upon dominant pigmentary anomalies and subdivisions with extracutaneous findings categorizes four prominent types of PPV (Table 24.3), with type

TABLE 24.3 Classification of PPV: classification is based on accompanying pigmented nevus

Type	Vascular malformation	Pigmentary nevus
I	Port-wine stain	Epidermal nevus
II	Port-wine stain	Dermal melanocytosis (\pm nevus anemicus)
III	Port-wine stain	Nevus spilus (\pm nevus anemicus)
IV	Port-wine stain	Dermal melanocytosis and nevus spilus (\pm nevus anemicus)

The designation 'a' and 'b' was given historically to denote the presence or absence of systemic findings.

II the most common. The pathogenesis of PPV has been proposed as a phenomenon called 'twin spotting'.¹³²

Numerous extracutaneous abnormalities may be seen, the most common being an overlap with Sturge–Weber syndrome, as well as Klippel–Trenaunay syndrome and melanosis oculi.^{133–138}

The differential diagnosis of PPV includes capillary malformation-macrocephaly syndrome and Beckwith–Wiedemann syndrome. Proteus syndrome may also be considered and is distinguished by the presence of overgrowth, asymmetry and gigantism. Treatment for certain birthmarks, with the aim of improving aesthetics, such as the port wine stain and dermal melanocytosis, can be accomplished with laser therapy.

Phakomatosis pigmentokeratotica

Phakomatosis pigmentokeratotica (PPK) describes the sporadic concurrence of a Blaschkoid epidermal nevus (organoid or sebaceous differentiation) with a cutaneous pigmentary anomaly such as nevus spilus.¹³⁹ The name rightly suggests an analogy with PPV and may occur due to the twin spotting genetic mechanism, and/or multilineage somatic mosaicism. In neonates and infants, the speckled lentiginous nevus may appear as a large CALM, prior to the development of 'speckles' and papules. Extracutaneous findings are usually present, including neurologic abnormalities (seizures, mental deficiency, hemiparesis and muscular weakness, dysesthesias), skeletal problems (including vitamin D-resistant rickets), and ophthalmologic alterations.^{139,140} Basal cell carcinoma and melanoma have been reported to arise in the nevus sebaceous and nevus spilus, respectively, and emphasizes the importance for long-term surveillance in these patients.¹⁴¹

Naegeli–Franceschetti–Jadassohn syndrome

Naegeli–Franceschetti–Jadassohn syndrome is an autosomal dominant subtype of ectodermal dysplasia syndrome characterized by the development of brown-gray reticulated pigmentation in early childhood without preceding inflammation.¹⁴² Pigmentation is localized on the abdomen in most cases but may be periorbital or perioral, or on the neck, flexures, groin or proximal extremities in some cases. Pigmentation gradually increases over the first decade of life and begins to fade after puberty. Sweating is markedly decreased in affected individuals, dermatoglyphics are often absent, and keratoderma of the palms and soles and dental anomalies can be seen. The syndrome is due to a mutation in the KRT14 gene located on

BOX 24.2 CUTANEOUS FEATURES OF XERODERMA PIGMENTOSUM

- Acute sun sensitivity: erythema (sunburn) and bullae
- Solar lentigines
- Hypopigmentation (achromic spots)
- Hyperkeratosis, dryness and scaling
- Telangiectasias
- Atrophy (thinning of the dermis, dermal elastosis)
- Benign and malignant neoplasms: basal cell carcinoma, squamous cell carcinoma, lentigo maligna, lentigo maligna melanoma, nodular melanoma, superficial spreading melanoma, actinic keratosis, keratoacanthoma, angioma, fibroma, sarcoma

17q11.2-q21 and is allelic to dermatopathia pigmentosa reticularis.¹⁴³

Striated hyperpigmentation of the torso

Horizontal thin stripes of hyperpigmentation (see Chapter 7) over the creases of the abdomen and extremities can be observed in the neonatal period.¹⁴⁴ This finding is typically transient and likely to result from shedding of hyperkeratotic skin after birth.

Congenital curvilinear palpable hyperpigmentation (sock-line bands, sock-line hyperpigmentation)

Congenital curvilinear palpable hyperpigmentation is a relatively recently described clinical finding on the posterior legs (usually bilateral posterior calves) of infants (see Fig. 8.27).¹⁴⁵ Involvement of the arms ('mitten-line hyperpigmentation') and heels ('heel-line hyperpigmentation') has also been described.^{146–148} The hyperpigmented to slightly erythematous plaques are often symmetric, palpable, curvilinear and semicircumferential. Macular hyperpigmentation is also common. The etiology of these lesions is unknown but trauma from tight socks or mittens has been proposed. The pigmentation resolves spontaneously over months to years. Because of the strikingly linear configuration of the lesions, this disorder can be confused with child abuse.

Spotty pigmentation – diffuse

XERODERMA PIGMENTOSUM

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder resulting in clinical and cellular sensitivity to ultraviolet (UV) light due to a decreased ability to repair DNA damage. XP patients experience cutaneous and ocular photosensitivity and are at increased risk for developing malignancy and pigmentary abnormalities (Box 24.2).

An infant born with XP will manifest skin changes after exposure to UV light, including sunburn after minimal sun exposure. Numerous pigmented macules (0.1–1 cm) will develop on sun-exposed skin, usually by the age of 2 years. These lesions may be brown, gray, or black (although a single lesion will be uniform in color) and may become so dense that they coalesce into larger pigmented patches. The amount of UV exposure correlates with the degree of pigmentation. Clinically, the macules resemble freckles but they are actually solar lentigines and they do not fade over time.¹⁴⁹ Hypopigmented or achromic spots develop and are thought to represent mutated

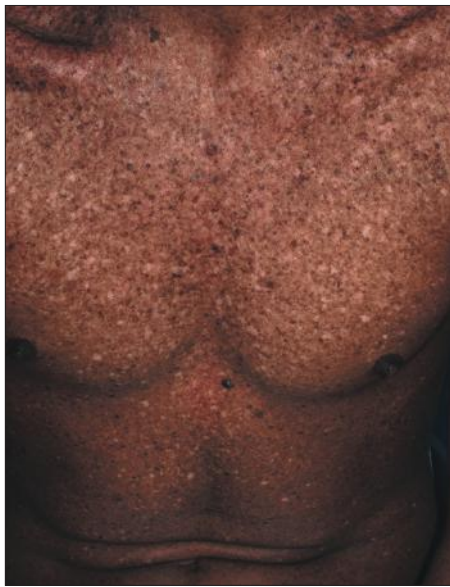


Figure 24.10 Extensive lentiginos and photodamage in a patient with xeroderma pigmentosum.

melanocytes that have lost the ability to synthesize melanin.^{150,151} Telangiectasias and atrophy arise with continued UV exposure as the skin undergoes actinic degeneration and these changes may be evident by the teenage years (Fig. 24.10). The skin becomes dry, scaly, and tight appearing. Cutaneous malignancies can arise in the pigmentary stage as well as the atrophic stage and include actinic keratoses, basal cell carcinoma, squamous cell carcinoma and melanoma as well as other rare skin tumors.^{152–154}

Ocular complications are commonly seen in XP patients as the eyelid skin, cornea and conjunctiva are exposed to sunlight. Ectropion or entropion, decreased lacrimation causing exposure keratitis, corneal edema, scarring and vascularization can develop.¹⁵⁰ Both benign and malignant neoplasms result, including squamous cell carcinoma and ocular melanoma. An increase in internal malignancies has been reported as well.¹⁵⁵ About 20% of patients with XP will develop primary neuronal degeneration resulting in neurologic abnormalities.^{155–157} These include sensorineural deafness, peripheral neuropathy, microcephaly, cerebral dysfunction (low intelligence, dementia, abnormal electroencephalogram), ventricular dilation and cortical atrophy, choreoathetosis, cerebellar ataxia, dysarthria and abnormal eye movements, and spasticity.¹⁵² The age of onset and rate of progression of the neurologic involvement is variable among patients.

XP has been reported worldwide and in all races.¹⁵⁰ It can be divided into two major forms: *nucleotide excision-repair pathway* defects and a *variant form* (XP-V), in which a defect in the *post-replication repair* of DNA exists.¹⁵² Designation of defects into complementation groups (XPA-G and XP-V) is based on in-vitro cell fusion studies. Different races may have a single dominant complementation group and some groups are made up of only a single kindred. Clinical features are determined by the amount of sun exposure, specific nature of the mutation and complementation group, and other environmental and unknown factors.

Clinical findings at birth in a neonate with XP are lacking and not evident until UV exposure and damage occurs. An

infant with significant and early sun burning should prompt further evaluation into photosensitivity syndromes. In addition to XP, other photosensitivity disorders should also be considered (Table 24.4). The differential of multiple pigmented macules includes Peutz-Jeghers syndrome, Carney complex, and LEOPARD syndrome. Histologic findings of cutaneous lesions are nondiagnostic and may show signs of severe photoaging, lentiginos or malignancy. Diagnosis confirmation can be done through functional testing to screen cells for abnormalities in DNA repair, but this is available on a research basis only. Commercial molecular genetic testing is available for only a limited number of subtypes and remaining genes may be tested through research laboratories. Testing for prenatal diagnosis on cultured cells from amniocentesis can be performed if a family history of XP exists.

Treatment and care. Management of individuals with XP involves genetic counseling, strict UV exposure avoidance, protective clothing and long hairstyles, sunscreen, sunglasses, protective window coatings and vitamin D supplementation. Skin examinations by the patient/family and dermatologist should be frequent so that malignancy and pre-malignant changes can be caught and treated early. Surgery techniques typically undertaken in normal individuals with skin cancer, such as cryotherapy, simple excision, electrodissection and curettage, Mohs micrographic surgery and the use of topical chemotherapeutic agents, are appropriate. The use of high-dose oral isotretinoin and acitretin has been reported to reduce certain types of new skin cancer formation in XP patients but use is often limited by side-effects, especially in children.^{158,159} Topical liposome-encapsulated endonuclease has also been reported to decrease the formation of actinic keratoses and basal cell carcinomas in XP patients.¹⁶⁰ Radiation therapy has been used successfully in treatment of aggressive skin cancers in patients with XP, as these patients tend to have a normal cellular and clinical response to ionizing radiation.¹⁶¹ Death may occur in individuals with XP due to cutaneous or internal malignancy or neurologic degeneration.

Post-inflammatory hyperpigmentation

Post-inflammatory hyperpigmentation (PIH) refers to the term used to describe brown, blue or grayish macules and patches after an exogenous or endogenous insult. PIH can be seen at birth and early on in life. Common exogenous causes in hospitalized infants include the use of tape, adhesive from monitoring leads, and mechanical trauma, which forms distinct patterns. More indistinct forms may result from endogenous inflammatory processes seen in neonates, such as seborrheic dermatitis and atopic dermatitis. In certain skin diseases such as morphea and lichen planus, PIH presents as a definitive morphological feature; however, almost all skin disease which results in inflammation can cause PIH. Those infants with darker skin types tend to be at higher risk for developing hyperpigmentation as compared to those with lighter skin.

A history of contact, trauma, or previous inflammatory process may be the clue to diagnosis. Epidermal melanocytes increase in size, number and melanin production following stimuli, including certain inflammatory diseases. When biopsied, the dermoepidermal junction and basal layer are disrupted by epidermal injury and melanin passes from its usual epidermal position to the dermis, subsequently engulfed by

TABLE
24.4

Photosensitivity disorders presenting in the neonatal and infantile period

Disorder	Defect	Findings
Cockayne syndrome	Homozygous or compound heterozygous mutation in the gene encoding the group 8 excision-repair cross-complementing protein (ERCC8) or group 6 excision-repair cross-complementing protein (ERCC6)	Cutaneous erythema with sun exposure in a butterfly distribution, atrophy, telangiectasias, neurologic impairment including ataxia and progressive deafness
Trichothiodystrophy (PIBIDS)	Mutation in helicase subunits ERCC2 and ERCC3	Photosensitivity, ichthyosis, brittle hair, impaired intelligence, decreased fertility and short stature
Congenital erythropoietic porphyria	Homozygous or compound heterozygous mutations in the uroporphyrinogen III synthase gene	Burning pain, blisters often with UV therapy for hyperbilirubinemia. Progressive scarring and disfigurement. Pink urine, red teeth, splenomegaly and anemia
Rothmund–Thomson syndrome	Compound heterozygous mutation in the DNA helicase gene RECQL4	Poikiloderma, alopecia, atrophic nails, congenital skeletal abnormalities, short stature, premature aging, and increased risk of malignant disease
Hartnup disorder	Mutations in the SLC6A19 gene	Pellagra-like light-sensitive rash, cerebellar ataxia, seizures, hypertonía, cognitive delay
Bloom syndrome	Mutations in DNA helicase RecQ protein-like-3	Poikiloderma, immunodeficiency, growth and skeletal abnormalities, predisposition to malignancy; and chromosomal instability



Figure 24.11 A premature infant with an ecchymotic plaque of the forehead due to pressure from the strap of a continuous positive airway pressure mask. This resulted in anetoderma.

macrophages to form melanophages.¹⁶² PIH takes time to resolve, as dermal melanin is slow to break down.

The differential diagnosis of PIH tends to be one of exclusion; certain patterns due to a particular contact are suggestive. Preceding history of an inflammatory event is helpful. A Wood's light may aid in determining the extent of pigment alteration as it accentuates epidermal melanin. In rare cases, a biopsy may be indicated and shows melanophages in the superficial dermis and basal layer along with a variable infiltrate of lymphohistiocytes around superficial blood vessels and in dermal papillae.

PIH may also be seen as a part of transient neonatal pustular melanosis (see [Chapter 7](#)) but, interestingly, a biopsy will not show dermal melanophages.¹⁶² Lesions of anetoderma of prematurity have been described to display ecchymotic-like blue-brown discoloration prior to the atrophic stage of these iatrogenic lesions.¹⁶³ Hyperpigmentation usually fades over time especially when pigment is epidermal.

Universal melanosis and progressive familial hyperpigmentation

A case of a healthy infant, born with white skin to Mexican parents, was described to develop progressive black pigmentation at 15 days of age that became diffuse by the age of 21 months, involving a portion of the palms and soles, nails, and oral and ocular mucosa.¹⁶⁴ The infant was otherwise well and developmentally normal. A skin biopsy revealed heavy hyperpigmentation of all epidermal layers and pigment-loaded histiocytes in the dermis. This condition was thought by the authors to be due to an overproduction of melanin and termed 'universal acquired melanosis' or 'carbon baby'. Other similar reports in the literature occurring in families have been termed, 'melanosis universalis hereditaria',¹⁶⁵ 'melanosis diffusa congenita',^{166,167} 'universal acquired melanosis',¹⁶⁴ 'familial progressive hyperpigmentation',¹⁶⁸ 'familial universal melanocytosis', or 'diffuse melanosis'.¹⁶⁹ It is unclear whether these cases represent the same entity or different disorders. In general, these progressive conditions tend to describe the onset of hyperpigmentation at birth or during early infancy that progresses in extent with age. Familial progressive hyperpigmentation was originally described as hyperpigmentation in a variety of variably sized dots, whirls, streaks, and patches, in contrast to universal acquired melanosis where the entire integument becomes black.^{164,168} Inheritance has been described in many of these similar disorders as autosomal dominant, possibly due to a heterozygous gain of function mutation in the KIT ligand gene.¹⁷⁰ Systemic manifestations do not occur, but irregular pigmentation of nails, oral and ocular mucosa and palms and soles have been seen. Histopathology of reported cases showed epidermal hypermelanosis with dispersed and widely distributed

TABLE
24.5

Disorders with congenital/infantile poikiloderma

Disorder	Cutaneous findings (in addition to poikiloderma)	Systemic associations	Inheritance and mutation
Poikiloderma with neutropenia	Photosensitivity, pachyonychia, keratoderma of palms/soles, calcinosis cutis, atrophic plaques	Growth retardation, recurrent pulmonary infections, dental defects, developmental delay, hepatosplenomegaly, non-cyclic neutropenia, elevated LDH levels, craniofacial dysmorphism, bone alterations, bone marrow failure, hematologic malignancy	AR; <i>C16orf57</i>
Rothmund–Thomson syndrome	Photosensitivity, atrophic nails, sparse hair, premature graying	Short stature, cataracts, bone abnormalities, hypogonadism, mental retardation, annular pancreas, skin cancer and osteosarcoma	AR; <i>RECQL4</i>
Bloom syndrome	Photosensitivity, blisters/fissures of lower lip, loss of lower eyelashes	Pre- and postnatal growth retardation, recurrent infections, endocrine abnormalities, gastroesophageal reflux, multiple malignancies	AR; <i>RECQL3</i>
Dyskeratosis congenita	Reticulated hyperpigmentation and atrophy, nail dystrophy, oral leukoplakia, alopecia, premature graying	Short stature, opportunistic infections, osteoporosis, conjunctival and anal mucosa leukoplakia and eye abnormalities, testicular hypoplasia, cryptorchidism, myelodysplasia, pancytopenia, cirrhosis, esophageal stricture, skin cancer, and hematologic malignancy	AR, AD, and XR; <i>DKC1</i> , <i>TERC</i> , <i>TERT</i> , <i>TINF2</i> , <i>NHP2</i> , <i>NOP10</i> , and <i>WRAP53</i>
Xeroderma pigmentosum	Photosensitivity resulting in sunburn and poikiloderma on exposed areas, nail abnormalities,	Skin cancer, neurologic degeneration, eye abnormalities (conjunctivitis, ectropion, entropion, keratitis, melanoma and squamous cell carcinoma)	AR; <i>XPA</i> , <i>ERCC3</i> (XP-B), <i>XPC</i> , <i>ERCC2</i> (XP-D), <i>DDB2</i> (XP-E), <i>ERCC4</i> (XP-F), <i>ERCC5</i> (XP-G), <i>ERCC1</i> and <i>POLH</i>
Kindler syndrome	Photosensitivity, neonatal trauma-induced skin blistering, poikiloderma on sun-exposed areas, nail abnormalities, hyperkeratosis of palms/soles	Gingivitis, periodontitis, orogenital leukokeratosis, conjunctivitis, digital webbing, pseudoainhum of toes, squamous cell carcinoma	AR; <i>FERMT1</i> (KIND1)

AR, autosomal recessive; AD, autosomal dominant; XR, X-linked recessive.

(Adapted from: Chantorn R, Shwayder T. Poikiloderma with neutropenia: report of three cases including one with calcinosis cutis. *Pediatr Dermatol* 2012; 29(4):463–472.)

melanosomes within keratinocytes. The clinical features as well as the histologic absence of melanin incontinence should differentiate these conditions from IP, Naegeli–Franceschetti–Jadassohn syndrome and LWNH.

Poikiloderma

Poikiloderma describes the cutaneous findings of atrophy, hyper- and hypopigmentation and telangiectasias that characterize several genetic disorders (Table 24.5, Fig 24.12). This clinical finding may be present at birth, during infancy, or develop in the first few years of life. Poikiloderma may present as a later finding in xeroderma pigmentosum, connective tissue disorders, Cockayne syndrome and Facioni anemia.¹⁷¹

The pathogenesis and etiology of poikiloderma are unknown, but commonly associated with UV exposure. The diagnosis is made by the typical clinical appearance of the reticulated eruption of telangiectasias and hypo- and hyperpigmentation. Histologic features depend on the severity and stage and include varying degrees of epidermal atrophy with hyperkeratosis, dilated vessels, hydropic degeneration of the basal layer, pigment-laden macrophages, and a dermal band-like or perivascular infiltrate of lymphocytes.¹⁷² The prognosis is dependant on the underlying associated disorder, and prompt recognition will aid in early diagnosis, monitoring and implementation of sun-avoidance behaviors.



Figure 24.12 A Native American girl with poikiloderma with neutropenia syndrome.

METABOLIC CAUSES

Addison disease and adrenocortical-unresponsiveness syndrome

Addison disease is adrenocorticoid deficiency resulting from dysfunction or destruction of the adrenal cortex. Glucocorticoid and mineralocorticoid production is affected. Although onset is usually in adulthood it may present earlier in congenital adrenal hyperplasia, due to a disorder of long-chain fatty acid metabolism, or polyglandular autoimmune syndromes.

Hyperpigmentation of skin and mucous membranes often precedes symptoms and is due to the stimulant effect of excess ACTH (adrenocorticotrophic hormone) and MSH (melanocyte-stimulating hormone) on melanocytes.¹⁷³ Pigmentation may present as diffuse tan, brown, or bronze darkening of skin surfaces, especially on sun-exposed areas, including nails and palmar creases, and blue-back patches on mucosal surfaces (including oral and anogenital mucosa). Associated signs and symptoms include weakness, weight loss, hypotension, hyponatremia, hyperkalemia, hypoglycemia and eosinophilia.

ACTH-insensitivity syndrome (or adrenocortical-unresponsiveness syndrome), a congenital insensitivity to functionally normal ACTH secretion, causes diffuse hyperpigmentation in the neonatal period and may precede systemic symptoms.^{174,175} Histologic findings of the hyperpigmentation are nondiagnostic and include increased epidermal melanin in keratinocytes and no increase in melanocytes.

LENTIGINES

LEOPARD syndrome (multiple lentigines syndrome, Moynahan syndrome)

The acronym LEOPARD was proposed by Gorlin to describe a heterogeneous syndrome that includes cutaneous lentigines, electrocardiographic conduction defects, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, retardation of growth and sensorineural deafness.¹⁷⁶ This rare autosomal dominant condition with variable expressivity involves cutaneous features as well as multiple organ systems. The originally described mutation responsible for LEOPARD syndrome (LS) was found on the gene PTPN 11, which has a dominant negative effect, interfering with growth factor/Erk-MAPK signaling.^{177,178} Additional mutations in BRAF and RAF1 have now been described and found to be associated with LS.^{179,180} LS is allelic to Noonan syndrome with many overlapping findings.

Lentigines can be noted during infancy as flat black-brown macules that increase in number until puberty, being generalized, with a predominance on the face, neck and upper trunk and usually sparing the mucous membranes. Lesions may not appear until childhood and the total number may be in the thousands; however, cases without lentigines have been reported. When biopsied the pigmented lesions reveal features of typical lentigines, displaying elongation of rete ridges, an increase in the concentration of melanocytes in the basal layer (without nests) with an increase in the amount of melanin in melanocytes and keratinocytes, as well as melanophages in the upper dermis.⁴² Café-au-lait macules are also seen in up to 70–80% of patients with LS and can predate the appearance of lentigines.¹⁸¹

In addition to lentigines, the majority (85%) of those with LS have heart defects, such as hypertrophic cardiomyopathy and

pulmonary valve stenosis.¹⁸² Congenital heart disease is often the most urgent medical issue during the first months of life and remains the leading medical issue for those patients that will eventually carry the diagnosis of LS.¹⁸³ Facial anomalies (mild or marked) are also invariably present in many patients with LS, although they are not diagnostically specific for the disorder.¹⁸³ Postnatal growth retardation, sensorineural hearing deficit and intellectual disability are less common associations but they are part of the classically described syndrome. Genital anomalies are seen predominantly in males and include gonadal hypoplasia, hypospadias, and delayed puberty. Various cranio-facial and skeletal anomalies have been described including short stature, pectus excavatum, kyphosis, ocular hypertelorism, and mandibular prognathism.

The diagnosis of LS is based on the cutaneous and systemic findings. Diagnostic criteria have been suggested: (1) if lentigines are present, at least two of the six other features are needed to make the diagnosis; (2) if lentigines are absent, an affected first-degree family member with LS and three of the six other features are needed for diagnosis.^{184,185} The differential diagnosis includes both generalized and patterned lentiginosis, namely Carney complex and Peutz–Jeghers syndrome (see below). The lentigines seen in XP can be widespread but are not present at birth and occur after UV exposure. In LS, the presence of lentigines is independent of UV exposure.

Treatment and care. In patients with lentigines noted at birth or during the neonatal period, evaluation should include a complete physical examination for associated extracutaneous findings, electrocardiogram (ECG), hearing evaluation, and other studies prompted by signs and symptoms. Abnormalities should be monitored by the appropriate specialist and genetic counseling should be provided. Treatment of lentigines has been attempted with cryotherapy and various lasers in some patients. The end results of these treatments are quite variable. It is generally not recommended in early childhood.^{186–189}

Carney complex (NAME/LAMB syndrome)

Several previous descriptions of the syndromes now consolidated under the term Carney complex represent various manifestations of this complex. These include NAME syndrome (nevi, atrial myxoma, myxoid neurofibromata, ephelides) and LAMB syndrome (lentigines, atrial myxoma, myxoid tumors, blue nevi).^{190–192} Carney complex is an autosomal dominant multiple endocrine neoplasia disorder characterized by lentigines, endocrine hyperactivity, cardiac myxomas and schwannomas.

The cutaneous findings in Carney complex include lentigines, café-au-lait macules, and blue nevi. Lentigines occur shortly after birth and are concentrated over the central facial area and can involve the mucosa. They can also extend to the neck, trunk, extremities and genitalia. Associated nevi can be congenital or arise later in infancy. Nontender dermal nodules, or cutaneous myxomas, do not often develop until the second decade of life and are typically located on the head and neck. Associated non-cutaneous findings in Carney complex include cardiac myxoma, endocrine diseases and tumors (Cushing syndrome, acromegaly), testicular tumors (in particular, Sertoli cell tumor), psammomatous melanotic schwannomas and possibly other benign and malignant neoplasms such as ductal adenoma of the breast.

Carney complex is due to a mutation in the *PRKAR1A* gene on chromosome 17q23.¹⁹³ This gene encodes the regulatory

subunit of protein kinase A and functions as a tumor-suppressor gene. Linkage to the short arm of chromosome 2 has also been described in 11 kindreds with clinical findings of Carney complex, indicating genetic heterogeneity.¹⁹⁴

Other multiple lentiginos syndromes need to be differentiated from Carney complex, including LEOPARD and Peutz–Jeghers syndromes. If a neonate has skin findings suggestive of Carney complex, evaluation by cardiology, endocrinology, and urology is warranted, and genetic counseling should be offered.¹⁹⁴

Spotty pigmentation – localized

Segmentally distributed spotty hyperpigmentation consists of groups of lentigines present in large numbers or in a distinctive localized distribution, with or without accompanying extracutaneous findings. Several designations exhibit clinical and semantic overlap, such as unilateral lentiginosis, segmental lentiginosis, lentiginous mosaicism and speckled giant café-au-lait macule. It is important to distinguish cutaneous-only conditions from familial lentiginosis syndromes or sporadic spotty pigmentation syndromes with possible associated anomalies. Histopathologic features of lentigines include increased numbers of melanocytes in the basal layer along with elongated epidermal rete ridges. Histopathology is not helpful in ascertaining a diagnosis. The following section describes particular entities with localized or segmental lentigines.

Centrofacial lentiginosis

Lentigines with involvement of the central face without further extension to other areas of the skin or mucosa have been termed ‘centrofacial lentiginosis’. Onset is usually in infancy and autosomal dominant inheritance is suggested. In adulthood, the lentigines often fade. Centrofacial lentiginosis may be associated with skeletal and bony abnormalities, neurologic manifestations, developmental and psychiatric symptoms and endocrine dysfunction.¹⁹⁵

Segmental lentiginosis (partial unilateral lentiginosis, lentiginous mosaicism)

Asymmetric segmental distribution of lentigines in large numbers usually designated to one side of the body has been termed segmental lentiginosis (also reported as partial lentiginosis, unilateral lentigines or agminated lentiginosis).¹⁹⁶ It has been suggested that some of these cases may actually represent a speckled lentiginous nevi, epidermal nevus or LWNH.^{197,198}

Another term, ‘partial unilateral lentiginosis’ (PUL), has been coined to describe small clustered hyperpigmented macules distributed in a unilateral limited area of the body (sometimes in a segmental pattern), usually involving the face, neck, and upper trunk.¹⁹⁹ These macules overlie normal skin and they have a sharp midline demarcation. Histologically lesions show features of lentigo simplex without nevus cells being present, although small nests of melanocytes have been described at the tips of the rete ridges, forming a ‘lentigo’ pattern.^{200,201} Lesions appear in childhood, as early as one year of age, but are rarely seen at birth. PUL has been associated rarely with central nervous system diseases (epilepsy, mental retardation, intracranial vascular malformations).^{202–204} Familial inheritance has not been described.

Segmental lentiginosis should be differentiated from other segmental disorders including speckled lentiginous nevus,



Figure 24.13 Peutz–Jeghers syndrome. Hyperpigmented labial macules.

segmental NF and agminated Spitz nevi. Wood’s light examination and skin biopsy may be helpful in these cases. Destruction of lentigines via laser or cryotherapy can be performed if desired.¹⁸⁹

Peutz–Jeghers syndrome

Peutz–Jeghers syndrome (PJS) is one of the most well-known familial lentiginosis syndromes. It is dominantly inherited and carries a risk of solid tumor malignancy.^{205,206} A key cutaneous diagnostic feature of PJS is dark brown-blue macules on the oral mucosa (buccal mucosa, palate, gingival), border of the lips (Fig. 24.13), and palms/soles, eyes, nares and perianal region.^{207,208} Pigmented bands in the nail plates can also be seen. The macules typically appear in childhood but can be present at birth and may fade in late adulthood. Mucosal lentigines tend not to fade. In addition, patients with PJS can have pigmented macules of the bowel mucosa, intestinal hamartomatous and adenomatous polyps (found in the jejunum, ileum, colon, rectum, stomach and duodenum). There is also an increased susceptibility to benign and malignant tumors including benign ovarian sex cord tumors, calcifying Sertoli tumors of the testes, cervical, breast, pancreatic, endometrial and gastrointestinal cancer.

PJS is mainly due to a heterozygous mutation in the serine threonine kinase *STK11/LKB1* gene, a tumor suppressor gene.^{209,210} Disease manifestations are triggered by the loss of the functional copy of the gene in somatic cells.

Histopathology of the cutaneous pigmented macules is typical for lentigines (see above). Abdominal pain, melena, or intussusception may be the presenting sign in individuals with intestinal involvement. The differential diagnosis of neonatal lentigines includes LEOPARD syndrome, Carney complex, and generalized lentiginosis. For patients with PJS, hematocrit and stool guaiacs are recommended in childhood and polyps may require surgical intervention for symptom relief. Referral to gastroenterology is needed for continued surveillance for malignancy of the GI tract, and medical screening with interval history and physical examinations of other associated organs to monitor for malignancy should be undertaken.

Bannayan–Riley–Ruvalcaba syndrome

Bannayan–Riley–Ruvalcaba (Riley–Smith, Bannayan–Zonana, and Ruvalcaba–Myhre–Smith syndromes) is an autosomal

dominant phenotypically variable disorder under the heading of ‘PTEN hamartoma tumor syndromes’ due to the discovery of mutation in the tumor suppressor gene *PTEN* in up to 60% of patients.²¹¹ Mutations in this gene are also described in Cowden syndrome and other related hamartoma syndromes.^{209,210} Vascular anomalies and intestinal hamartomatous polyps have also been described.

Lentigines, 2–6 mm in size commonly occur on the glans and shaft of the penis or on the vulva of females. These may be present at birth or infancy, or develop during childhood and adolescence.^{212,213} Other cutaneous findings may include single or multiple café-au-lait macules, subcutaneous lipomas, vascular anomalies, facial papules (displaying features of trichilemmomas and verrucae),²¹⁴ oral and perianal papillomas, acrochordons, acral keratoses and acanthosis nigricans.

Noncutaneous findings in BRRS include the common findings of macrocephaly (without ventricular enlargement) that may be noted at birth or infancy. About half of the patients will have neurologic abnormalities including hypotonia, delayed psychomotor development, mental deficiency and seizures.²¹⁴ Visceral lipomas, hamartomatous intestinal polyps (45% of patients),²¹⁵ skeletal abnormalities and joint hyperextensibility may also be seen. Retinal abnormalities such as prominent Schwalbe lines and corneal nerves may be noted in 35% of patients as well as pseudopapilledema.^{216,217} A myopathic process described in BRRS has shown a lipid storage myopathy on muscle biopsy, predominantly in enlarged type 1 skeletal muscle fibers.^{218,219} Thyroiditis and thyroid neoplasms have been reported.²¹⁵

BRRS is allelic to Cowden syndrome with many overlapping cutaneous and systemic features; however, Cowden syndrome has a later age of onset, usually in adulthood. Patients with Peutz–Jeghers syndrome do not have the genital distribution of lentigines as in BRRS. Proteus syndrome, another multiple hamartoma syndrome, presents with pigmented lesions consistent with epidermal nevi and Blaschkoid nevoid hypermelanosis, which should be easily distinguishable from BRRS. Genital lentigines in BRRS may be subtle and easily overlooked. Recognition of the disorder should prompt referrals for management of associated systemic conditions.

PIGMENTARY VARIATIONS

Dyschromatosis

The dyschromatoses are a group of disorders described by both cutaneous macular hyperpigmentation and hypopigmentation and a lack of atrophy or telangiectasias as seen in poikiloderma. Macules are irregular in shape and small in size. The dyschromatoses have been divided into two major forms, designated ‘dyschromatosis symmetrica hereditaria’ and ‘dyschromatosis universalis hereditaria’.

Dyschromatosis symmetrica hereditaria (DSH) is used to describe patients with both hyper- and hypopigmented macules on the extremities, in particular, the dorsal hands and feet, sparing the palms and soles and mucosa. Most cases have been described in Japan and China and show an autosomal dominant inheritance.²²⁰ The majority of patients will develop skin findings before the age of 6 years.²²⁰ Facial lesions can resemble ephelides and these lesions do not fade over time. DSH tends to be found in primarily sun-exposed areas but there is no evidence of photosensitivity in these patients. DSH can be

caused by a heterozygous mutation in the adenosine deaminase, RNA-specific gene *DSRAD* on chromosome 1q21.^{221,222}

Dyschromatosis universalis hereditaria (DUH) consists of hyperpigmented and hypopigmented macules in a diffuse pattern, mainly truncal, reported in families with possible autosomal dominant and recessive inheritance. The majority of patients present by age 6 years or younger as in DSH, and cases noted at birth have been reported.²²⁰ Mucous membrane lesions and lesions on the palms and soles may occur in DUH. Rare noncutaneous associations with deafness, short stature, as well as hematologic and tryptophan metabolic abnormalities have been reported in patients with possible DUH.^{223,224}

Pigmentary demarcation lines

Pigmentary demarcation lines are natural pigmentary boundaries mostly described and seen in black and Asian patients. These lines have been categorized into five groups, designated A–E.²²⁵ Group A (anterior brachial) designates lines along the upper limb with variable trans-pectoral extension;²²⁶ group B lines are along the medial lower limbs; group C lines are paired lines in median or paramedian courses on the chest with midline abdominal extension; group D lines describe a postero-median demarcation, and group E are bilaterally symmetric, obliquely orientated hypopigmented macules on the chest/periareolar region.

Groups A and C are most commonly described and distinct. Group A lines were described in 20%, 29%, and 37% of examined black patients by Futcher, Vollum, and Selmanowitz, respectively, and 6% of Japanese patients.^{225–227} The degree of overall skin pigmentation did not seem to correlate with incidence of A lines. Lines tended to be more apparent in the older population. Group C lines were noted in more than 30% of black patients.^{228,229} Group E lines have been described more often in children (69%) and seem to become less noticeable over time.²³⁰

CONGENITAL MELANOCYTIC NEVI

Congenital melanocytic nevi (CMN) are hamartomatous proliferations of neuroectoderm elements comprised mainly of melanocytes with variable numbers of nevus cells and other neural elements. Their presence is determined in utero and hence many are clinically apparent at birth. Pigmented lesions clinically resembling CMN have been reported to be present in 1–6% of neonates and the majority occur sporadically.^{39,231–235} The terms ‘tardive CMN’, ‘early onset nevi’, and ‘congenital nevus-like nevi’ have been used to represent nevi with clinical and histologic features of CMN that were not clinically apparent at birth but occurring often within the first 2–3 years of life.²³⁶

Historically, CMN have been classified according to their predicted largest diameter in adulthood (predicted adult diameter or PAS).^{237,238} The most commonly used classification designates small CMN as <1.5 cm, medium sized CMN between 1.5 and 19.9 cm, and large CMN ≥20 cm (Fig. 24.14). CMN measuring at least 50 cm in size are sometimes referred to as ‘giant nevi’. Although a nevus may on rare occasion grow disproportionately to the growth of the child during early infancy, most CMN will grow in proportion.²³⁹ A new, more detailed classification system (Table 24.6) has been proposed that may eventually help to better identify patients at greatest risk for developing melanoma and/or neurocutaneous melanocytosis.

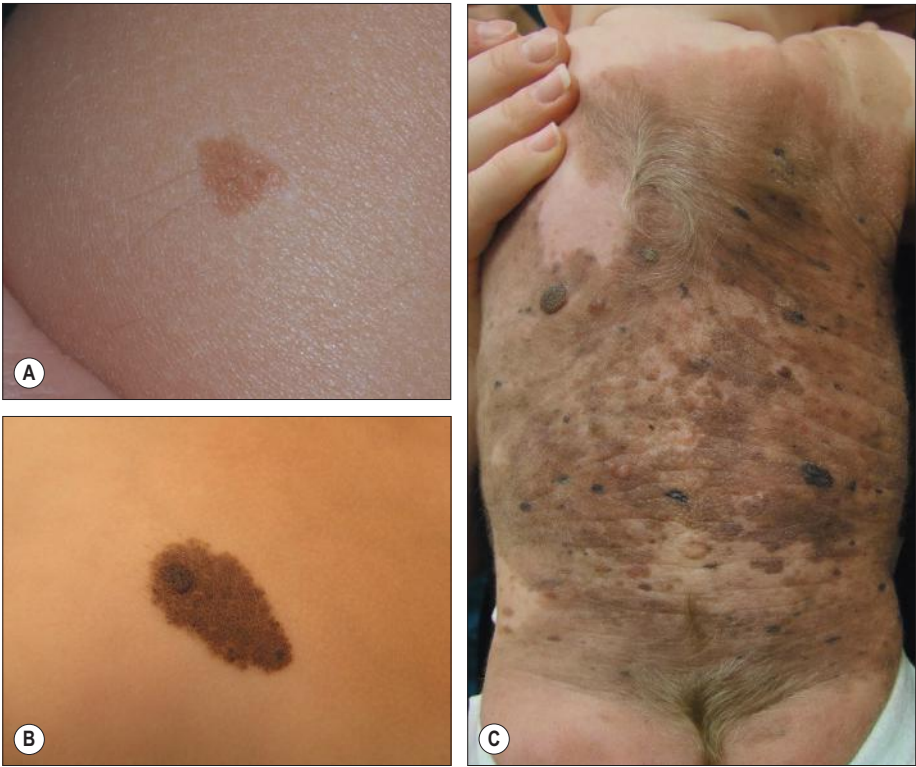


Figure 24.14 Small (A), medium (B), and giant congenital melanocytic nevi (C).

TABLE 24.6 Proposed new classification of congenital melanocytic nevi (CMN)		
CMN parameter	Terminology	Definition
CMN projected adult size	Small CMN	<1.5 cm
	Medium CMN	
	M1	1.5–10 cm
	M2	>10–20 cm
	Large CMN	
	L1	>20–30 cm
	L2	>30–40 cm
	Giant CMN	
	G1	>40–60 cm
	G2	>60 cm
	Multiple medium CMN	≥3 medium CMN without a single, predominant CMN
CMN localization ^a		
CMN of head	Face, scalp	
CMN of trunk	Neck, shoulder, upper back, middle back, lower back, breast/chest, abdomen, flank, gluteal region, genital region	
CMN of extremities	Upper arm, forearm, hand, thigh, lower leg, foot	
No. of satellite nevi ^b	S0	No satellites
	S1	<20 satellites
	S2	20–50 satellites
	S3	>50 satellites
Additional morphologic characteristics	C0, C1, C2	none, moderate, marked color heterogeneity
	R0, R1, R2	none, moderate, marked surface rugosity
	N0, N1, N2	none, scattered, extensive dermal or subcut nodules
	H0, H1, H2	none, notable, marked hypertrichosis ('hairiness')

^aOne or more of these localizations should be used to describe preponderant area of involvement.
^bRefers to number of satellites within first year of life; in case this number is not available, actual number should be mentioned.
(Adapted from: Krengel S, Scope A, Dusza SW, Vonthein R, Marghoob AA. New recommendations for the categorization of cutaneous features of congenital melanocytic nevi. *J Am Acad Dermatol* 2012; 68(3):441–451.)



Figure 24.15 Small congenital nevus with even coloration and borders, and a mammillated surface texture.



Figure 24.16 Medium congenital nevus with prominent hair growth.

It also provides nomograms that can assist clinicians in easily predicting the final adult diameter of a nevus examined at any point during childhood.

In general, CMN may be macules, patches, papules or plaques at birth. Coloration may be quite homogenous throughout or heterogeneous with shades of brown, black, red, or blue. The texture may be smooth, nodular or cobblestone-like and hair may or may not be present at birth and may or may not develop as the child ages and can be fine or coarse in texture when present. A cerebriform, or *cutis verticis gyrata*, appearance may be present in large scalp CMN. Neurotization and lipomatous changes are also features that can be seen, particularly in larger CMN. Atrophic CMN can also occur. Over time, CMN tend to evolve and may become darker or lighter, may become more or less heterogeneous in color and the surface texture may change. CMN can also develop superimposed nodules and papules. The CMN-involved skin can be xerotic and eczematous resulting in symptoms of pruritus. The dermoscopic pattern of most CMN found on the head/neck/trunk is globular and those found on the lower extremities tend to exhibit a reticular pattern.²⁴⁰

Making the diagnosis of a CMN is most often done by clinical appearance and dermoscopic features. The larger CMN can easily be diagnosed based solely on their size. For smaller CMN, their history of presence since birth, surface topography, presence of hypertrichosis or globular dermoscopic morphology can assist in diagnosis. When biopsied, the histological features of CMN are similar to those found in common acquired nevi which arise later in life; however, CMN tend to have a greater cellularity with deeper extension of nevus cells into the deep dermis and subcutis and cells extend along adnexal structures such as hair follicles and around blood vessels and nerves.²⁴¹ Depth of nevus cell infiltration tends to correlate with the size of CMN.²⁴²

Although most CMN occur sporadically, rare familial clustering of giant CMN has been observed.^{243,244} The concept of paradigmatic inheritance has been introduced as a possible explanation of the familial occurrence in an otherwise sporadic condition.

Small and medium congenital melanocytic nevi

Small and medium CMN are often tan to brown in color and oval-shaped with well-demarcated borders (Fig. 24.15). Lesions

may develop a mammillated surface and hypertrichosis over time (Figs 24.15, 24.16). The risk of melanoma development in small and medium CMN is thought to be less than 1% over a lifetime and these melanomas generally develop well after puberty (Table 24.7).^{245–259} Melanomas arising in small and medium CMN tend to develop at the dermoepidermal junction and at the peripheral or leading edge of the CMN, making them more readily recognized by patients and clinicians.²⁶⁰ Although rare prepubertal cases of melanoma arising in medium CMN have been described, no cases of melanoma in medium-sized CMN were described in four large prospective and retrospective studies with significant patient follow-up.^{253–255,257}

Large congenital melanocytic nevi

Large CMN occur in 1 in 20 000 individuals and are obvious at birth, most commonly covering an aspect of the trunk and less common on the head, neck and extremities.⁹³ Affected areas of large CMN have been designated as a ‘cape’, ‘bathing trunk’ or ‘garment’ CMN due to their distribution, respectively. Lesions may have irregular or geographic borders. In about 75% of cases, multiple small CMN will accompany the large CMN; these additional CMN noted at birth and which may gradually increase in number over time have been historically termed ‘satellite nevi’. These additional multiple CMN should be noted in both size and number as a larger number of satellite nevi have been correlated with neurological anomalies.

At birth or within the first few weeks of life, transient erosions or ulcerations may develop over large CMN due to increased skin fragility during this period (Fig. 24.17).^{261,262} Healing usually occurs over days to weeks. Also notable during the infantile period are rapidly growing ‘proliferative nodules’ within the CMN that mimic melanoma but show benign histological features.^{263,264} Evaluation of these specimens by a dermatopathologist with expertise in pigmented lesions is recommended to avoid a misdiagnosis of melanoma.²⁶⁰ The use of comparative genomic hybridization (CGH) has been used to support the benign nature of these proliferative nodules and this can be performed on paraffin-embedded specimens.^{265,266} Significant lightening of pigmentation in large CMN can also be seen in the first few years of life.²⁶⁷ Over time, areas of large CMN may undergo neurotization, which may present as soft, plexiform neurofibroma-like plaques and nodules, especially

TABLE
24.7Studies of melanoma risk in congenital melanocytic nevi (CMN) (includes longitudinal studies of ≥ 40 patients with CMN followed for a mean of ≥ 3 years and published since 1990)

Reference	Number of patients	Mean age at entry, years	Mean follow-up time, years	Number of patients with melanoma (% of total)	Locations of primary melanomas
Prospective cohort studies of large CMN					
Ruiz-Maldonado et al. 1992	80	1.7	4.7	2 (2.5)	All cutaneous/axial
Egan et al. 1998	46	8.4	7.3	2 (4.3)	All cutaneous/axial
Hale et al. 2005	170 ^b	1.2	5.3	4 (2.4) ^c	Extracutaneous (3), unknown primary (1)
Internet registry-based studies of large CMN^d					
Bett, 2005	861	NA	(5.6) ^e	16 (1.9) Garment CMN: 15/525 (2.9) Head/extremity CMN: 1/336 (0.3)	Cutaneous/axial (14), extracutaneous (1), unknown primary (1)
Ka et al. 2005	379	8	2–6	0 (0)	–
Retrospective cohort studies of large CMN					
Foster et al. 2001	46	0.5	5	0 (0)	–
Lovett et al. 2009	52	1.3	7.4	0 (0)	–
Yun et al. 2012	131	10.3	4.8	3/131 (2.3)	Cutaneous (2), extracutaneous (1)
Retrospective cohort study of medium-sized CMN					
Sahin et al. 1998	227	19	6.7	0 (0)	–
Retrospective cohort study of CMN of all sizes					
Swerdlow et al. 1995	265	(84% <15 years)	24	≥ 20 cm CMN: 2 ^e /26 (7.6) 5–19 cm CMN: 0/84 (0) 1–4.9 cm CMN: 0/155 (0)	All cutaneous/axial
Fernandes et al. 2009	74	4	6	≥ 20 cm CMN: 0/5 (0) <20 cm CMN: 0/69 (0)	–
Prospective cohort study of CMN of all sizes					
Dawson et al. 1996	133	3.1	3.4	0 (0)	–
Kinsler et al. 2009	349 ^f	2.9	9.2	≥ 20 cm CMN: 4 ^e /122 (3.3) 1–19 cm CMN: 0/214 (0) Multiple CMN: 1/13 (7.7)	Cutaneous/axial (2), CNS (2), unknown (1)
Retrospective population-based studies of CMN of all sizes					
Berg and Lindelöf, 2003	3922 ^g	0	10 (median)	0 (0)	–
Zaal et al. 2005	3929 ^h	19	4.7	≥ 20 cm CMN: 4/320 (1.3) <20 cm CMN: 11/3609 (0.3)	Cutaneous/axial (9), cutaneous/extremity (6)

^aData from references 245–259.^bAmong 35 additional patients who were not followed prospectively, five developed melanoma (all within truncal CMN).^cAll melanomas developed in association with CMN measuring >39 cm (Hale et al. 2005)²⁴⁷; >40 cm (Swerdlow et al. 1995)²⁵⁴; >60 cm (Kinsler et al. 2009).²⁵⁷^dInformation obtained by voluntary report of members of support groups for patients with congenital melanocytic nevi (not confirmed by the physician/medical record).^eMelanomas diagnosed prior to entry into the registry were not excluded.^fIncludes 48 patients who were not followed prospectively.^gData from the Swedish Medical Birth Register and Swedish Cancer Register.^hHistologically proven CMN entered into a comprehensive pathology archive in the Netherlands.

NA, not available.

(Modified from: Price HN, Schaffer JV. Congenital melanocytic nevi-when to worry and how to treat: Facts and controversies. Clin Dermatol 2010; 28(3):293–302 and Schaffer JV, Price HN, Orlow SJ. Congenital melanocytic nevi. In: Rigel DS, Robinson JK, Ross M, et al., eds. Cancer of the skin. Edinburgh: Elsevier; 2011:255.)

around the lower back, flanks, and buttocks and groin (Fig. 24.18). Neurotized scalp nevi can be associated with alopecia and cerebriform folds that resemble cutis verticis gyrata. Over time, several large CMN on the scalp have been reported to spontaneously lighten and regress;^{268,269} however, further histologic studies on these scalp nevi showed the presence of nevus cells within the deep dermis and around adnexal structures.²⁶⁹

The halo phenomenon and vitiligo-like changes can also occur in large CMN.^{270–272} A ‘desmoplastic hairless hypopigmented’ type CMN is a rare variant of CMN and is characterized by a woody induration, alopecia, progressive loss of pigmentation and associated intense pruritus.^{273,274}

The absolute risk of melanoma development (cutaneous or extracutaneous) in large CMN is approximately 2–5% over



Figure 24.17 Large congenital nevus with erosions and nodularity.



Figure 24.18 Giant congenital nevus with soft plaques and nodules.

one's lifetime, considering prospective and retrospective cohort studies with significant follow-up.²⁵⁴ About 50% of these melanomas occur in the first 5 years of life.^{246,247,275} Cutaneous melanomas tend to arise deep in the dermis or subcutaneous tissues of a large CMN, making early detection difficult. Cutaneous melanomas reported over the past decades in patients with large CMN were seen more commonly in those over the trunk, as compared to the head/neck and extremities.^{247,248,257,276} However, this difference may be attributable entirely on the melanocytic burden since CMN on the torso are usually larger (>40 cm PAS) and bulkier than CMN on other sites. The number of satellite nevi does not portend a higher risk for developing cutaneous melanoma but having >20 satellite lesions does increase the risk for neurocutaneous melanocytosis (NCM) and central nervous system melanoma. Other malignancies such as liposarcomas, rhabdomyosarcomas, and malignant peripheral nerve sheath tumors have been described in association with large CMN.²⁷⁷ No reliable case of melanoma arising within a satellite nevus has been reported.

Magnetic resonance imaging (MRI) with contrast of the brain and spine is recommended for any individual with multiple CMN, or a large CMN with >20 satellite nevi, as those with

≥20 satellite nevi are five times more likely to have neurocutaneous melanocytosis (see below) than those with fewer.²⁷⁸ Individuals with large CMN, >40 cm adult size, or those with a CMN over the posterior axis (in select studies) may also be at increased risk for NCM.^{267,278} In addition, CMN overlying the lower back/sacrum area may be associated with the tethered cord syndrome, which can be detected via MRI scanning. It is estimated that about 4% of these 'high-risk' CMN individuals will develop symptomatic NCM and prognosis is generally poor even without melanoma development.^{247,279,280} Ideally, MRI should be done in the first 4–6 months of life, prior to myelination of the brain, which may make it more difficult to observe the melanin signal. The typical radiologic appearance of melanocytic deposits is T1 hyperintensity and/or T2 hypointensity, overlying the cerebellum, leptomeninges, amygdala and temporal lobes.^{250,267,281,282} Other CNS tumors and malformations found during brain and spine imaging of CMN patients have included Dandy–Walker malformations, Chiari I malformations, posterior fossa cysts, spinal lipomas, arachnoid cysts and tethered spinal cord.^{250,267,283–286}

Recently, facial morphology analysis found that patients with CMN had a characteristic facies, with 74% of the children in the series having at least three typical features: wide or prominent forehead, apparent hypertelorism, eyebrow variants, periorbital fullness, small/short nose, narrow nasal bridge, broad nasal tip, broad or round face, full cheeks, prominent premaxilla, prominent/long philtrum and everted lower lip.²⁸⁷ Thus, the term congenital melanocytic nevus syndrome was recommended to describe these associations.²⁸⁸

MANAGEMENT AND TREATMENT OF CMN

Small and medium CMN

Prophylactic excision of small and medium CMN is arguable, as recent data have failed to show an appreciable risk of melanoma in patients with small and medium CMN and the risk of malignancy prior to puberty is quite low.^{258,289} Regardless of future risk of melanoma in these patients, removal may be justifiable if concerning signs of malignancy have developed, a significant psychosocial burden is present, chronic family or patient anxiety for melanoma development exists, or the lesion is one where long-term observation will prove difficult.²⁶⁰

Removal of small CMN and smaller medium-sized CMN is usually easily accomplished by simple elliptical excision followed by primary closure. Larger medium-sized CMN may require staged excision, tissue expansion, flap reconstruction or skin graft in order to achieve an acceptable cosmetic and functional outcome.

Large CMN

Neonatal and infantile erosions or ulceration overlying a large CMN are often treated successfully with conservative wound care. Pruritus and overlying eczematous changes in these nevi may be treated with topical corticosteroids, bland emollients and oral antihistamines when appropriate. Intractable pruritus over localized areas may also be relieved by surgical excision of limited areas.

Absolute indications for removal of large CMN include the development of malignancy and metastatic melanoma with an unknown primary. Relative indication for treatment include: (1) to decrease melanocytic burden, especially in those

lesions that are thick, rugous, and heterogeneous in color; (2) lesions present in covered areas that may be clinically difficult to follow; (3) improvement in cosmesis and psychosocial benefits, and (4) symptoms such as intractable pruritus or functional impairment.

Removal of large CMN is often desired in attempts to prevent melanoma development within the lesion. There are no studies to date that clearly support the notion that early removal of a large CMN will prevent melanoma development. Also, complete removal of all nevus cells is often impossible as these cells often involve deeper structures such as fascia and muscle. In addition, removal of the main nevus would not prevent melanoma development in noncutaneous sites, such as the CNS. The use of skin grafts and development of hypertrophic scars may also obscure the detection of melanoma underneath the defect when nevus cells still remain. However, excision of those nevi that are symptomatic, bulky and cumbersome, psychologically distressing and/or functionally limiting may be beneficial despite the risks of surgery.

Elective surgical procedures are often initiated during the first 2 years of life due to the increased elasticity of the skin and the lower risk of abnormal scarring.^{260,290} It is not uncommon for subsequent repigmentation to occur within or around the resultant surgical scar, as the full extent of the CMN is often not apparent until after this age.^{257,260,291} Numerous surgical treatment choices are available for excision and reconstruction of CMN: staged excision with tissue expansion and flap reconstruction, excision with skin grafting, cultured epithelial grafts or artificial skin substitutes.^{291,292} Surgical excision of CMN of the scalp, in particular, should be debated as there is a low risk of malignant transformation at this location and the possibility of regression or significant lightening in the first few years of life may supersede any cosmetic concerns in this area.²⁶⁸

Dermabrasion is a procedure performed early in life to remove the epidermis and superficial dermis resulting in a decreased density in hair and lightening in pigmentation. This procedure runs the risk of hypertrophic scarring and resultant skin fragility and does not eliminate the risk of melanoma, as nevus cells in deeper tissues are still present. Curettage done during the first few weeks of life takes advantage of a natural cleavage plane between normal dermis and dermis containing nevomelanocytes, leaving a sclerotic and dense connective tissue. The risks of anesthesia this early in life as well as potential abnormal scarring, skin fragility and difficulty in monitoring for melanoma due to the resultant scar should be taken into consideration with this technique.

A number of ablative (carbon dioxide) and non-ablative pigment-specific lasers (ruby, alexandrite, Nd:YAG) have been used in attempts to destroy nevus cells and melanosomes (Q-switched), lighten pigmentation and remove excessive hair from nevi that are not amenable to surgical resection.^{10,293,294} Repigmentation, scarring and the need for numerous treatments (often with general anesthesia) are common. An increased incidence of melanoma in those patients treated with laser therapy has not been reported.

Parents should be counseled to perform skin examinations to monitor for focal worrisome changes. Serial clinical photographs, dermoscopy and palpation of these lesions may be beneficial for clinicians following patients with any size CMN. With large CMN, lifelong monitoring is mandatory, both with parent (then self-skin) examinations and by an experienced

dermatologist. In addition to physical examination and photography, examination of lymph nodes and a thorough review of systems may aid physicians in early detection of melanoma.

NEUROCUTANEOUS MELANOCYTOSIS

In addition to melanoma, patients with large CMN and multiple smaller CMN are also at risk for developing neurocutaneous melanocytosis (NCM), estimated to occur in 7% of individuals born with large CMN.²⁸⁶ NCM is a proliferation of melanocytes in the leptomeninges or brain parenchyma due to abnormal migration of melanocyte precursors in the embryonal neuroectoderm.^{281,295} Although these deposits are generally benign, symptoms such as hydrocephalus and seizures can occur, and malignant transformation to melanoma has been reported in approximately 2.3% of affected patients.²⁴⁷ NCM has been classically defined by Kadonaga and Frieden as (1) large or multiple CMN (≥ 3) in association with meningeal melanocytosis or melanoma, (2) no evidence of cutaneous melanoma, except patients in whom the examined areas of the meningeal lesions are histologically benign, and (3) no evidence of meningeal melanoma, except patients in whom the examined areas of the cutaneous lesions are histologically benign.²⁹⁵

Patients with radiologically apparent NCM should be divided into symptomatic and asymptomatic NCM. Based on previous studies, approximately 60–70% of those individuals with NCM are symptomatic and symptoms usually will manifest before the age of 5.^{250,251,279,286} Patients typically present with hydrocephalus, seizures, and other signs indicating increased cranial pressure such as headaches and vomiting. Mild to severe developmental delay and abnormal tone have also been described in children with high-risk CMN.^{267,286} Asymptomatic NCM (positive MRI but not clinical symptoms attributed to NCM) has been diagnosed in up to 30% of patients with high-risk CMN and the percentage of patients that may eventually develop symptoms from NCM is currently unknown.

Obtaining a screening MRI scan of the brain and spine in patients at high risk for NCM should be considered in the first 4–6 months of life; any patient that develops neurologic symptoms should also undergo imaging and evaluation by a neurologist. Patients with asymptomatic NCM should also be followed by a neurologist, often on a yearly basis or more frequently if concerns exist. The need for subsequent MRI in those asymptomatic patients is not clear; however, most experts do not recommend further imaging unless symptoms arise.²⁸⁶ Patients with significant symptomatic NCM should consider forgoing elective surgical removal of the CMN until prognosis is clear.

Differential diagnosis

The differential diagnosis of small and medium CMN includes smooth muscle hamartoma or Becker's nevus, mastocytoma, variant of dermal melanocytosis, and café-au-lait macules. Large CMN may be confused with a plexiform neurofibroma in neurofibromatosis type 1 syndrome.²⁹⁶ Histologic evaluation, dermoscopy and the development of typical CMN features over time may clarify the diagnosis.

CONGENITAL MELANOMA

Congenital melanoma, defined as melanoma present at birth, is an exceedingly rare congenital cancer. As of 2004, approximately 13 cases of congenital (seen at birth or first day of life)

melanoma were reported in the literature as well as an additional 14 cases seen from 2 weeks of life to 12 months of age.²⁹⁷ Incidence and mortality rate from congenital melanoma are unknown. Melanoma may be primarily fetal (de novo), develop from transplacental metastases from metastatic maternal melanoma, or develop within a CMN or leptomeningeal melanosis while in utero. Occasionally tumors may be diagnosed during gestation via ultrasound.²⁹⁸ Darkly pigmented nodules and plaques with or without ulceration may be the initial signs seen at birth. Excised specimens should be examined by an experienced dermatopathologist as to not misdiagnose a proliferative nodule as a melanoma, especially within a CMN.

SPECKLED LENTIGINOUS NEVUS AND OTHER SUBTYPES OF CMN

A ‘speckled lentiginous nevus’ (SLN) or ‘nevus spilus’, consisting of a tan café-au-lait-like macule background patch with superimposed darker macules and papules, is designated by most as a subtype of CMN and is evident in approximately 2% of adults.^{236,299} The background patch is usually noted at birth or shortly thereafter. Often the superimposed macules and papules of various colors develop progressively over time. The superimposed lesions can consist of lentigines to junctional, compound or intradermal nevi, as well as Spitz nevi and blue nevi (see Fig. 24.21). Histologic features of congenital nevi and increased hair growth may be evident. It was reported that some lesions will acquire a more CMN appearance over time and others will exist as a ‘hybrid’ lesion with areas of SLN appearing as classic CMN and others as typical SLN.³⁰⁰

Two distinct subtypes of SLN have been described: macular and papular SLN.³⁰¹ The macular SLN is characterized by a tan brown background with darker flat speckles (Fig. 24.19). A tan brown background superimposed by papules or nodules of multiple melanocytic nevi characterizes papular SLN. SLN can involve many skin sites, but the trunk and lower limbs tend to



Figure 24.19 Speckled lentiginous nevus (nevus spilus) of the axilla (mimicking axillary freckling of NF-1).

be involved more frequently.³⁰² Size designation for SLN have included those used for traditional CMN (small, medium, large, and giant CMN) as well as descriptions of zosteriform and Blaschkoid forms.^{302–305}

Rare cases of melanoma have been reported in SLN, although there may be an increased predominance in the macular subtype.^{108,301,306–311} The risk of melanoma development in SLN is currently unknown but reported cases tend to occur in adulthood (mean age 49 years) with an equal gender and race distribution and in larger nevi.³¹²

Other associations with SLN include the association of the macular subtype with phacomatosis pigmentovascularis (type III),³¹³ whereas phacomatosis pigmentokeratotic and SLN syndrome are seen in association with the papular SLN subtype.^{301,314,315} SLN syndrome is rare but may be suspected in those patients with a segmental papular SLN with ipsilateral musculoskeletal or neurologic disturbances, including muscle weakness, dysesthesias and hyperhidrosis.³¹⁴

The differential diagnosis of SLN includes CALM, light-colored CMN, Becker's nevus, and the segmental form of NF-1. Speckling is uncommonly seen in congenital nevi and Becker's nevus. A Wood's light may be used to discern the presence or absence of a background patch, which may be subtle in lightly pigmented individuals.

Treatment and care

The management of patients with SLN, is similar to CMN and should consist of clinical long-term follow-up, especially during adulthood, even though the risk of melanoma is low. Any concerning changes or atypical features should be biopsied.

SPITZ NEVI (SPINDLE AND EPITHELIOID NEVI)

Spitz nevi are unique melanocytic nevi that occur most often in the first and second decades of life, although congenital cases are well described. They usually present as round, symmetric papules, pink to brown or brown-black in color and hairless with a smooth or verrucous surface.^{316,317} Typical locations for pediatric Spitz nevi include the head, neck and extremities. Dermoscopic evaluation of pink or hypopigmented Spitz nevi often reveals a dotted or polymorphous vascular pattern (Fig. 24.20). The pigmented Spitz nevi usually manifest a globular pattern, negative network pattern or starburst pattern – a highly characteristic pattern defined by numerous regular streaks found at the periphery of the lesion (Fig. 24.22).³¹⁸

Multiple Spitz nevi are uncommon and can occur in groups, so called ‘agminated’ Spitz nevi, or rarely as disseminated discrete lesions. Agminated Spitz nevi may be present on a background of tan-brown skin or hypopigmented skin, or on a background of normal skin.^{319,320} The lesions may be present at birth or acquired. The most common location for agminated Spitz nevi in children is the face (cheeks), and several to over 100 lesions may be present.³²¹ Inciting factors for agminated and disseminated Spitz nevi in children have included trauma and sunburns.^{321–323} Spitz nevi may also develop within SLN or compound nevi. None of these clinical variants has been associated with a poor prognosis.³²⁴

Initially deemed ‘juvenile melanomas’, classic Spitz nevi have histopathological features that when present are reassuring to the clinician.³²⁵ These include a symmetrical contour, maturation with progressive depth, an even base and discrete junctional nests. Kamino bodies can be seen along with mild



Figure 24.20 Hypopigmented Spitz nevus with corresponding dermoscopy

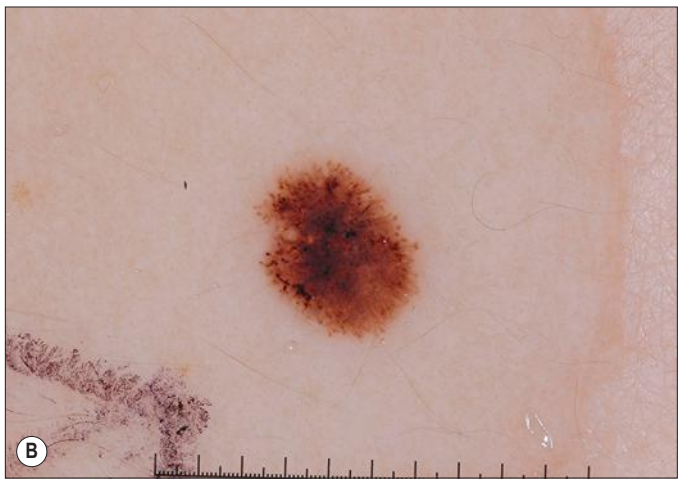


Figure 24.22 Pigmented Spitz nevus with dermoscopy demonstrating characteristic starburst pattern.

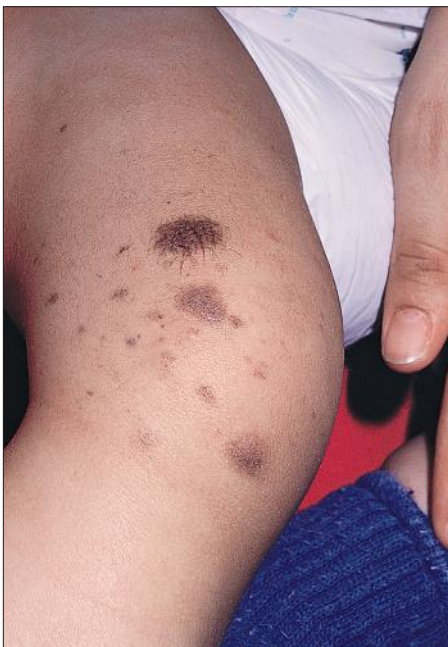


Figure 24.21 Nevus spilus with faint brown hyperpigmented background and darker brown nevi within the affected area.

pagetoid scatter in the center of the lesion and superficial mitoses. Most Spitz nevi are compound, and less commonly junctional or dermal in type.³²⁶ Confusing nomenclature regarding lesions with concerning architectural and cytologic features as 'Spitz tumors,' 'STUMP' (Spitzoid tumors of uncertain malignant potential), 'atypical Spitz nevus' and 'Spitzoid melanomas' have made both clinicians and pathologists manage these atypical lesions more aggressively in children and adults. Histologic criteria for these atypical Spitz nevi and Spitzoid melanoma are not well established, and a significant amount of interobserver variability in their interpretation exists, even among expert dermatopathologists.^{242,327,328}

The differential diagnosis of Spitz nevi includes intradermal melanocytic nevus, pyogenic granuloma, hemangioma, wart, melanoma, juvenile xanthogranuloma and mastocytoma. In cases of multiple Spitz nevi, melanoma with cutaneous in-transit disease or disseminated cutaneous metastases must be excluded.

Treatment and care

The management of pediatric Spitz nevi is surrounded by controversy and there is no clear consensus. It is generally accepted that classic Spitz nevi (those with typical clinical and dermoscopic features and history) are benign; however, as their natural history is not well described, many lesions concerning for Spitz nevi are biopsied to confirm the diagnosis. Those Spitz nevi with classic and un concerning features, if not completely

excised, have a small chance of recurrence, making long-term follow-up difficult. Thus conservative re-excision with 1–2 mm margins should be considered.³²⁹ A minority of clinicians will monitor clinically apparent Spitz and find that many nevi regress over time.^{330,331} However, long-term observation, perhaps starting in infancy, may cause significant anxiety for the family and relies on compliance of the patient and family and the comfort of the clinician in monitoring these lesions. Those lesions with the so-called diagnosis of atypical Spitzoid nevus/tumor or STUMP, should be conservatively excised to diminish the risk of recurrence. CGH and additional histochemical studies now available may favor a more benign diagnosis, which

is reassuring, as Spitz nevi have been found to have different molecular alterations in comparison to melanoma.³³² Those lesions deemed as pediatric Spitzoid melanomas are often treated as adult melanomas with wide excision based on the lesion depth, and evaluation of the draining lymph node basis by sentinel lymph node biopsy when indicated. Long-term follow-up of these patients with incompletely excised Spitz nevi and those with atypical and Spitzoid melanoma lesions should be carried out.

Access the full reference list at ExpertConsult.com 

KEY REFERENCES

11. Polder KD, Landau JM, Vergilis-Kalner JJ, et al. Laser eradication of pigmented lesions: a review. *Dermatol Surg* 2011;37(5):572–95.
18. Denayer E, Chmara M, Brems H, et al. Legius syndrome in fourteen families. *Hum Mutat* 2011;32(1):E1985–98.
114. Molho-Pessach V, Schaffer JV. Blaschko lines and other patterns of cutaneous mosaicism. *Clin Dermatol* 2011;29(2):205–25.
133. Chhajed M, Pandit S, Dhawan N, et al. Klippel–Trenaunay and Sturge–Weber overlap syndrome with phakomatosis pigmentovascularis. *J Pediatr Neurosci* 2010;5(2):138–40.
137. Jeon SY, Ha SM, Ko DY, et al. Phakomatosis pigmentovascularis Ib with left-sided hemihypertrophy, interdigital gaps and scoliosis: A unique case of phakomatosis pigmentovascularis. *J Dermatol* 2013;40(1):78–9.
155. Bradford PT, Goldstein AM, Tamura D, et al. Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair. *J Med Genet* 2011;48(3):168–76.
183. Digilio MC, Lepri F, Baban A, et al. RASopathies: Clinical diagnosis in the first year of life. *Mol Syndromol* 2011;1(6):282–9.
212. Tan MH, Mester J, Peterson C, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. *Am J Hum Genet* 2011;88(1):42–56.
243. de Wijn RS, Zaal LH, Hennekam RC, et al. Familial clustering of giant congenital melanocytic nevi. *J Plast Reconstr Aesthet Surg* 2010;63:906–13.
287. Kinsler VA, Abu-Amro S, Budd P, et al. Germline melanocortin-1-receptor genotype is associated with severity of cutaneous phenotype in congenital melanocytic nevi: a role for MC1R in human fetal development. *J Invest Dermatol* 2012;132:2026–32.

REFERENCES

- Alper J, Holmes LB, Mihm MC Jr. Birthmarks with serious medical significance: nevocellular nevi, sebaceous nevi, and multiple café au lait spots. *J Pediatr* 1979;95(5 Pt 1):696–700.
- Whitehouse D. Diagnostic value of the café-au-lait spot in children. *Arch Dis Child* 1966;41(217):316–19.
- McLean DJ, Gallagher RP. 'Sunburn' freckles, café-au-lait macules, and other pigmented lesions of schoolchildren: the Vancouver Mole Study. *J Am Acad Dermatol* 1995;32(4):565–70.
- Shah KN. The diagnostic and clinical significance of café-au-lait macules. *Pediatr Clin North Am* 2010;57(5):1131–53.
- Rivers JK, MacLennan R, Kelly JW, et al. The eastern Australian childhood nevus study: prevalence of atypical nevi, congenital nevus-like nevi, and other pigmented lesions. *J Am Acad Dermatol* 1995;32(6):957–63.
- Crowe FW, Schull WJ. Diagnostic importance of café-au-lait spot in neurofibromatosis. *AMA Arch Intern Med* 1953;91(6):758–66.
- Bell SD, MacDonald DM. The prevalence of café-au-lait patches in tuberous sclerosis. *Clin Exp Dermatol* 1985;10(6):562–5.
- Raulin C, Schönemark MP, Greve B, et al. Q-switched ruby laser treatment of tattoos and benign pigmented skin lesions: a critical review. *Ann Plast Surg* 1998;41(5):555–65.
- Shimbashi T, Kamide R, Hashimoto T. Long-term follow-up in treatment of solar lentigo and café-au-lait macules with Q-switched ruby laser. *Aesthetic Plast Surg* 1997;21(6):445–8.
- Carpo BG, Grevelink JM, Grevelink SV. Laser treatment of pigmented lesions in children. *Semin Cutan Med Surg* 1999;18(3):233–43.
- Polder KD, Landau JM, Vergilis-Kalner JJ, et al. Laser eradication of pigmented lesions: a review. *Dermatol Surg* 2011;37(5):572–95.
- Metzker A, Morag C, Weitz R. Segmental pigmentation disorder. *Acta Derm Venereol* 1983;63(2):167–9.
- Hogeling M, Frieden IJ. Segmental pigmentation disorder. *Br J Dermatol* 2010;162(6):1337–41.
- Jacobs AH, Cahn RL. Birthmarks. *Pediatr Ann* 1976;5(12):743–58.
- Obringer AC, Meadows AT, Zackai EH. The diagnosis of neurofibromatosis-1 in the child under the age of 6 years. *Am J Dis Child* 1989;143(6):717–19.
- Korf BR. Diagnostic outcome in children with multiple café au lait spots. *Pediatrics* 1992;90(6):924–7.
- Brems H, Chmara M, Sahbatou M, et al. Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. *Nat Genet* 2007;39(9):1120–6.
- Denayer E, Chmara M, Brems H, et al. Legius syndrome in fourteen families. *Hum Mutat* 2011;32(1):E1985–98.
- Pasmant E, Sabbagh A, Hanna N, et al. SPRED1 germline mutations caused a neurofibromatosis type 1 overlapping phenotype. *J Med Genet* 2009;46(7):425–30.
- Arnsmeier SL, Riccardi VM, Paller AS. Familial multiple café au lait spots. *Arch Dermatol* 1994;130(11):1425–6.
- Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the alpha subunit of the stimulatory G protein of adenyl cyclase in McCune–Albright syndrome. *Proc Natl Acad Sci USA* 1992;89(11):5152–6.
- Weinstein LS, Shenker A, Gejman PV, et al. Activating mutations of the stimulatory G protein in the McCune–Albright syndrome. *N Engl J Med* 1991;325(24):1688–95.
- Weinstein LS. G(s)alpha mutations in fibrous dysplasia and McCune–Albright syndrome. *J Bone Miner Res* 2006;21(Suppl. 2):P120–4.
- Levine MA. The McCune–Albright syndrome. The whys and wherefores of abnormal signal transduction. *N Engl J Med* 1991;325:1738–40.
- Shenker A, Weinstein LS, Moran A, et al. Severe endocrine and nonendocrine manifestations of the McCune–Albright syndrome associated with activating mutations of stimulatory G protein GS. *J Pediatr* 1993;123:509–18.
- Olsen BR. A rare disorder, yes; an unimportant one, never. *J Clin Invest* 1998;101:1545–6.
- Happle R. The McCune–Albright syndrome: a lethal gene surviving by mosaicism. *Clin Genet* 1986;29(4):321–4.
- Rieger E, Kofler R, Borkenstein M, et al. Melanotic macules following Blaschko's lines in McCune–Albright syndrome. *Br J Dermatol* 1994;130(2):215–20.
- Lumbroso S, Paris F, Sultan C. McCune–Albright syndrome: molecular genetics. *J Pediatr Endocrinol Metab* 2002;15(Suppl. 3):875–82.
- de Sanctis C, Lala R, Matarazzo P, et al. McCune–Albright syndrome: a longitudinal clinical study of 32 patients. *J Pediatr Endocrinol Metab* 1999;12(6):817–26.
- Bowerman JE. Polyostotic fibrous dysplasia with oral melanotic pigmentation. *Br J Oral Surg* 1969;6(3):188–91.
- Gorlin RJ, Chaudhry AP. Oral melanotic pigmentation in polyostotic fibrous dysplasia, Albright's syndrome. *Oral Surg Oral Med Oral Pathol* 1957;10(8):857–62.
- Yoshimoto M, Nakayama M, Baba T, et al. A case of neonatal McCune–Albright syndrome with Cushing syndrome and hyperthyroidism. *Acta Paediatr Scand* 1991;80:984–7.
- Aarskog D, Tveteraas E. McCune–Albright's syndrome following adrenalectomy for Cushing's syndrome in infancy. *J Pediatr* 1968;73:89–96.
- Silva ES, Lumbroso S, Medina M, et al. Demonstration of McCune–Albright mutations in the liver of children with high gammaGT progressive cholestasis. *J Hepatol* 2000;32(1):154–8.
- Roth JG, Esterly NB. McCune–Albright syndrome with multiple bilateral café au lait spots. *Pediatr Dermatol* 1991;8(1):35–9.
- Cordova A. The Mongolian spot: a study of ethnic differences and a literature review. *Clin Pediatr (Phila)* 1981;20(11):714–19.
- Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics* 1976;58(2):218–22.
- Rivers JK, Frederiksen PC, Dibdin C. A prevalence survey of dermatoses in the Australian neonate. *J Am Acad Dermatol* 1990;23(1):77–81.
- Hidano A. Persistent Mongolian spot in the adult. *Arch Dermatol* 1971;103(6):680–1.
- Teekhasaene C, Ritch R, Rutnin U, et al. Ocular findings in oculodermal melanocytosis. *Arch Ophthalmol* 1990;108(8):1114–20.
- Elder DE, Elenitas R, Murphy G, et al. Benign pigmented lesions and malignant melanoma. In: Elder DE, Elenitas R, Johnson BL, et al, editors. *Lever's histopathology of the skin*. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 715–25.
- Hanson M, Lupski JR, Hicks J, et al. Association of dermal melanocytosis with lysosomal storage disease: clinical features and hypotheses regarding pathogenesis. *Arch Dermatol* 2003;139(7):916–20.
- Weissbluth M, Esterly NB, Caro WA. Report of an infant with GM1 gangliosidosis type I and extensive and unusual mongolian spots. *Br J Dermatol* 1981;104(2):195–200.
- Beratis NG, Varvarigou-Frimas A, Beratis S, et al. Angiokeratoma corporis diffusum in GM1 gangliosidosis, type I. *Clin Genet* 1989;36(1):59–64.
- Esterly NB, Weissbluth M, Caro WA. Mongolian spots and GM1 type I gangliosidosis. *J Am Acad Dermatol* 1990;22(2 Pt 1):320.
- Beattie RM, Harvey D. Extensive and unusual Mongolian blue spots in a child with GM1 gangliosidosis type one. *J R Soc Med* 1992;85(9):574–5.
- Tang TT, Esterly NB, Lubinsky MS, et al. GM1-gangliosidosis type 1 involving the cutaneous vascular endothelial cells in a black infant with multiple ectopic Mongolian spots. *Acta Derm Venereol* 1993;73(6):412–15.
- Camur S, Coşkun T, Kiper N. Alpha-mannosidosis: the first Turkish case. *Acta Paediatr Jpn* 1995;37(2):230–2.
- Grant BP, Beard JS, de Castro F, et al. Extensive mongolian spots in an infant with Hurler syndrome. *Arch Dermatol* 1998;134(1):108–9.
- Tanner M, Proksch E, Christophers E. [Von Recklinghausen neurofibromatosis and dermal melanocytic nevi]. *Hautarzt* 1995;46(4):263–7.
- Mihara M, Nakayama H, Aki T, et al. Cutaneous nerves in café au lait spots with white halos in infants with neurofibromatosis. An electron microscopic study. *Arch Dermatol* 1992;128(7):957–61.
- Kurata S, Ohara Y, Itami S, et al. Mongolian spots associated with cleft lip. *Br J Plast Surg* 1989;42(6):625–7.
- Igawa HH, Ohura T, Sugihara T, et al. Cleft lip mongolian spot: mongolian spot associated with cleft lip. *J Am Acad Dermatol* 1994;30(4):566–9.
- Hisano A, Kasai K, Fukuzumi Y. An analysis of 114 patients with dermal melanocytosis on the trunk and extremities. *Scand J Plast Reconstr Surg Hand Surg* 1999;33(2):231–6.
- Kagami S, Asahina A, Uwajima Y, et al. Treatment of persistent Mongolian spots with Q-switched alexandrite laser. *Lasers Med Sci* 2012;27(6):1229–32.
- Kagami S, Asahina A, Watanabe R, et al. Laser treatment of 26 Japanese patients with Mongolian spots. *Dermatol Surg* 2008;34(12):1689–94.
- Kopf AW, Weidman AI. Nevus of Ota. *Arch Dermatol* 1962;85:195–208.
- Dorsey CS, Montgomery H. Blue nevus and its distinction from Mongolian spot and the nevus of Ota. *J Invest Dermatol* 1954;22(3):225–36.
- Mishima Y, Mevorah B. Nevus Ota and nevus Ito in American Negroes. *J Invest Dermatol* 1961;36:133–54.

61. Hidano A, Kajima H, Ikeda S, et al. Natural history of nevus of Ota. *Arch Dermatol* 1967;95(2):187-95.
62. De Las Heras C, Gonzalez P, Manzano RM, et al. Nevus de Ota bilateral. *Acta Dermosifiliogr* 1991;82:245-7.
63. Dutton JJ, Anderson RL, Schelper RL, et al. Orbital malignant melanoma and oculodermal melanocytosis: report of two cases and review of the literature. *Ophthalmology* 1984;91(5):497-507.
64. Patel BC, Egan CA, Lucius RW, et al. Cutaneous malignant melanoma and oculodermal melanocytosis (nevus of Ota): report of a case and review of the literature. *J Am Acad Dermatol* 1998;38(5 Pt 2):862-5.
65. Khawly JA, Imami N, Shields MB. Glaucoma associated with the nevus of Ota. *Arch Ophthalmol* 1995;113(9):1208-9.
66. Teekhasaene C, Ritch R, Rutnin U, et al. Glaucoma in oculodermal melanocytosis. *Ophthalmology* 1990;97(5):562-70.
67. Shaffer D, Walker K, Weiss GR. Malignant melanoma in a Hispanic male with nevus of Ota. *Dermatology* 1992;185(2):146-50.
68. Balmaceda CM, Fetell MR, O'Brien JL, et al. Nevus of Ota and leptomeningeal melanocytic lesions. *Neurology* 1993;43(2):381-6.
69. Theunissen P, Spincemaille G, Pannebakker M, et al. Meningeal melanoma associated with nevus of Ota: case report and review. *Clin Neuropathol* 1993;12(3):125-9.
70. Noriega-Sanchez A, Markand ON, Herndon JH. Oculocutaneous melanosis associated with the Sturge-Weber syndrome. *Neurology* 1972;22(3):256-62.
71. Furukawa T, Igata A, Toyokura Y, Ikeda S. Sturge-Weber and Klippel-Trénaunay syndrome with nevus of Ota and Ito. *Arch Dermatol* 1970;102(6):640-5.
72. Gupta A, Ram J, Jain IS. Nevus of Ota associated with neurofibromatosis. *Ann Ophthalmol* 1986;18(4):154-5.
73. Reinke RT, Haber K, Josselson A. Ota nevus, multiple hemangiomas, and Takayasu arteritis. *Arch Dermatol* 1974;110(3):447-50.
74. Whyte MP, Dekaban AS. Familial cerebellar degeneration with slow eye-movements, mental deterioration and incidental nevus of ota (oculo-dermal melanocytosis). *Dev Med Child Neurol* 1976;18(3):373-80.
75. Piercecchi-Marti MD, Mohamed H, Liprandi A, et al. Intracranial meningeal melanocytoma associated with ipsilateral nevus of Ota. Case report. *J Neurosurg* 2002;96(3):619-23.
76. Alvarez-Cuesta CC, Raya-Aguado C, Vázquez-López F, et al. Nevus of Ota associated with ipsilateral deafness. *J Am Acad Dermatol* 2002;47(Suppl. 5):S257-9.
77. Reed WB, Sugarman GI. Unilateral nevus of Ota with sensorineural deafness. *Arch Dermatol* 1974;109(6):881-3.
78. Botticelli AR, Villani M, Angiari P, et al. Meningeal melanocytoma of Meckel's cave associated with ipsilateral Ota's nevus. *Cancer* 1983;51(12):2304-10.
79. Sagar HJ, Ilgren EB, Adams CB. Nevus of Ota associated with meningeal melanosis and intracranial melanoma. Case report. *J Neurosurg* 1983;58(2):280-3.
80. Taylor CR, Flotte TJ, Gange RW, et al. Treatment of nevus of Ota by Q-switched ruby laser. *J Am Acad Dermatol* 1994;30(5 Pt 1):743-51.
81. Shimbashi T, Hyakusoku H, Okinaga M. Treatment of nevus of Ota by Q-switched ruby laser. *Aesthetic Plast Surg* 1997;21(2):118-21.
82. Liu J, Ma YP, Ma XG, et al. A retrospective study of q-switched alexandrite laser in treating nevus of ota. *Dermatol Surg* 2011;37(10):1480-5.
83. Chang CJ, Kou CS. Comparing the effectiveness of Q-switched Ruby laser treatment with that of Q-switched Nd:YAG laser for oculodermal melanosis (Nevus of Ota). *J Plast Reconstr Aesthet Surg* 2011;64(3):339-45.
84. Landau JM, Vergilis-Kalner I, Goldberg LH, et al. Treatment of Nevus of Ota in Fitzpatrick skin type VI with the 1064-nm QS Nd:YAG laser. *Lasers Surg Med* 2011;43(2):65-7.
85. Trindade F, Santonja C, Requena L. Bilateral nevus of Ito and nevus spilus in the same patient. *J Am Acad Dermatol* 2008;59(2 Suppl. 1):S51-2.
86. Hidano A, Kajima H, Endo Y. Bilateral nevus Ota associated with nevus Ito. A case of pigmentation on the lips. *Arch Dermatol* 1965;91(4):357-9.
87. van Krieken JH, Boom BW, Scheffer E. Malignant transformation in a naevus of Ito. A case report. *Histopathology* 1988;12(1):100-2.
88. Wise SR, Capra G, Martin P, et al. Malignant melanoma transformation within a nevus of Ito. *J Am Acad Dermatol* 2010;62(5):869-74.
89. Martínez-Peñuela A, Iglesias ME, Mercado MR, et al. [Malignant transformation of a nevus of Ito: description of a rare case]. *Actas Dermosifiliogr* 2011;102(10):817-20.
90. Ferrari A, Lozzi GP, Fargnoli MC, et al. Dermoscopic evolution of a congenital combined nevus in childhood. *Dermatol Surg* 2005;31(11 Pt 1):1448-50.
91. Kawasaki T, Tsuboi R, Ueki R, et al. Congenital giant common blue nevus. *J Am Acad Dermatol* 1993;28:653-4.
92. Botev IN. Giant congenital cellular blue naevus of the scalp and cranium. *Br J Plast Surg* 1998;51:410-11.
93. Castilla EE, da Graca Dutra M, Orioli-Parreiras IM. Epidemiology of congenital pigmented naevi: I. Incidence rates and relative frequencies. *Br J Dermatol* 1981;104:307-15.
94. Fuchs F, Guillot E, Salama S, et al. Giant congenital scalp blue nevus, a neonatal case report. *Eur J Obstet Gynecol Reprod Biol* 2007;132:243-4.
95. Golden N, Maliawan S, Mulyadi K. Cellular blue naevus of the scalp with brain invasion. *J Clin Neurosci* 2000;7:453-4.
96. Madaree A, Ramdial PK, Du Treu M. Giant congenital naevus of the scalp and cranium: case report and review of the literature. *Br J Plast Surg* 1997;50:20-5.
97. Hendrickson MR, Ross JC. Neoplasms arising in congenital giant nevi: morphologic study of seven cases and a review of the literature. *Am J Surg Pathol* 1981;5:109-35.
98. Bennaceur S, Fraitag S, Teillac-Hamel D, et al. [Giant congenital blue nevus of the scalp]. *Ann Dermatol Venerol* 1996;123:807-10.
99. Nakano S, Kinoshita K, Morita Y, et al. Cellular blue nevus of the scalp associated with intracranial involvement. *Surg Neurol* 1987;27:553-7.
100. Wetherington GM, Norins AL, Sadove AM. Locally invasive cellular blue nevus of the scalp. *Plast Reconstr Surg* 1987;79:114-17.
101. Iemoto Y, Kondo Y. Congenital giant cellular blue nevus resulting in dystocia. *Arch Dermatol* 1984;120:798-9.
102. Silverberg GD, Kadin ME, Dorfman RF, et al. Invasion of the brain by a cellular blue nevus of the scalp. A case report with light and electron microscopic studies. *Cancer* 1971;27:349-55.
103. Findler G, Hoffman HJ, Thomson HG, et al. Giant nevus of the scalp associated with intracranial pigmentation. Case report. *J Neurosurg* 1981;54:108-12.
104. Marano SR, Brooks RA, Spetzler RF, et al. Giant congenital cellular blue nevus of the scalp of a newborn with an underlying skull defect and invasion of the dura mater. *Neurosurgery* 1986;18:85-9.
105. Serarslan G, Yaldiz M, Verdi M. Giant congenital cellular blue naevus of the scalp with disseminated common blue naevi of the body. *J Eur Acad Dermatol Venerol* 2009;23:190-1.
106. Pittman JL, Fisher BK. Plaque-type blue nevus. *Arch Dermatol* 1976;112(8):1127-8.
107. Betti R, Inselvini E, Crosti C. Blue nevi and basal cell carcinoma within a speckled lentiginous nevus. *J Am Acad Dermatol* 1999;41(6):1039-41.
108. Cox NH, Malcolm A, Long ED. Superficial spreading melanoma and blue naevus within naevus spilus - ultrastructural assessment of giant pigment granules. *Dermatology* 1997;194(3):213-16.
109. Davis DG, Shaw MW. An unusual human mosaic for skin pigmentation. *N Engl J Med* 1964;270:1384-9.
110. Fryns JP, Lemaire J, Timmermans J, et al. The association of hemifacial microsomia, homolateral micro/anophthalmos, hemihypotrophy, dental anomalies, submucous cleft palate, CNS malformations and hypopigmented skin lesions following Blaschko's lines in two unrelated female patients. Further evidence for a lethal mutation surviving in mosaic form in 'hypomelanosis of Ito'. *Genet Couns* 1993;4(1):63-7.
111. Sybert VP, Pagon RA, Donlan M, et al. Pigmentary abnormalities and mosaicism for chromosomal aberration: association with clinical features similar to hypomelanosis of Ito. *J Pediatr* 1990;116(4):581-6.
112. Jenkins D, Martin K, Young ID. Hypomelanosis of Ito associated with mosaicism for trisomy 7 and apparent 'pseudomosaicism' at amniocentesis. *J Med Genet* 1993;30(9):783-4.
113. Lombillo VA, Sybert VP. Mosaicism in cutaneous pigmentation. *Curr Opin Pediatr* 2005;17:494-500.
114. Molho-Pessach V, Schaffer JV. Blaschko lines and other patterns of cutaneous mosaicism. *Clin Dermatol* 2011;29(2):205-25.
115. Findlay GH, Moores PP. Pigment anomalies of the skin in the human chimaera: their relation to systematized naevi. *Br J Dermatol* 1980;103(5):489-98.
116. Kalter DC, Griffiths WA, Atherton DJ. Linear and whorled nevoid hypermelanosis. *J Am Acad Dermatol* 1988;19(6):1037-44.
117. Di Lernia V. Linear and whorled hypermelanosis. *Pediatr Dermatol* 2007;24(3):205-10.
118. Alimurung FM, Lapenas D, Willis I, et al. Zebra-like hyperpigmentation in an infant with multiple congenital defects. *Arch Dermatol* 1979;115(7):878-81.
119. Nehal KS, PeBenito R, Orlow SJ. Analysis of 54 cases of hypopigmentation and hyperpigmentation along the lines of Blaschko. *Arch Dermatol* 1996;132(10):1167-70.
120. Van Gysel D, Oranje AP, Stroiink H, et al. Phacomatosis pigmentovascularis. *Pediatr Dermatol* 1996;13:33-5.
121. Hartmann A, Hofmann UB, Hoehn H, et al. Postnatal confirmation of prenatally

- diagnosed trisomy 20 mosaicism in a patient with linear and whorled nevoid hypermelanosis. *Pediatr Dermatol* 2004;21(6):636–41.
122. Verghese S, Newlin A, Miller M, et al. Mosaic trisomy 7 in a patient with pigmentary abnormalities. *Am J Med Genet* 1999; 87(5):371–4.
 123. Kubota Y, Shimura Y, Shimada S, et al. Linear and whorled nevoid hypermelanosis in a child with chromosomal mosaicism. *Int J Dermatol* 1992;31(5):345–7.
 124. Komine M, Hino M, Shiina M, et al. Linear and whorled naevoid hypermelanosis: a case with systemic involvement and trisomy 18 mosaicism. *Br J Dermatol* 2002;146(3):500–2.
 125. Kuwahara RT, Henson T, Tunca Y, et al. Hyperpigmentation along the lines of Blaschko with associated chromosome 14 mosaicism. *Pediatr Dermatol* 2001;18(4):360–1.
 126. Devriendt K, Matthijs G, Meireleire J, et al. Skin pigment anomalies and mosaicism for a double autosomal trisomy (48, XX, +18, +20). *Genet Couns* 1998;9(4):283–6.
 127. Akiyama M, Aranami A, Sasaki Y, et al. Familial linear and whorled nevoid hypermelanosis. *J Am Acad Dermatol* 1994;30(5 Pt 2):831–3.
 128. IIPC The International Incontinentia Pigmenti Consortium. Genomic rearrangement in NEMO impairs NF-kappa-B activation and is a cause of incontinentia pigmenti. *Nature* 405:466–72, 2000.
 129. Landy SJ, Donnai D. Incontinentia pigmenti (Bloch–Sulzberger syndrome). *J Med Genet* 1993;30:53–9.
 130. Parrish JE, Scheuerle AE, Lewis RA, et al. Selection against mutant alleles in blood leukocytes is a consistent feature in incontinentia pigmenti type 2. *Hum Molec Genet* 1996;5:1777–83.
 131. Ruiz-Maldonado R, Tamayo L, Laterza AM, et al. Phacomatosis pigmentovascularis: a new syndrome? Report of four cases. *Pediatr Dermatol* 1987;4(3):189–96.
 132. Happle R. Phacomatosis pigmentovascularis revisited and reclassified. *Arch Dermatol* 2005;141(3):385–8.
 133. Chhajed M, Pandit S, Dhawan N, et al. Klippel–Trenaunay and Sturge–Weber overlap syndrome with phacomatosis pigmentovascularis. *J Pediatr Neurosci* 2010;5(2):138–40.
 134. Finklea LB, Mohr MR, Warthan MM, et al. Two reports of phacomatosis pigmentovascularis type IIb, one in association with Sturge–Weber syndrome and Klippel–Trenaunay syndrome. *Pediatr Dermatol* 2010;27(3):303–5.
 135. Turk BG, Turkmen M, Tuna A, et al. Phacomatosis pigmentovascularis type IIb associated with Klippel–Trenaunay syndrome and congenital triangular alopecia. *J Am Acad Dermatol* 2011;65(2):e46–9.
 136. Cho S, Choi JH, Sung KJ, et al. Phacomatosis pigmentovascularis type IIB with neurologic abnormalities. *Pediatr Dermatol* 2001;18(3):263.
 137. Jeon SY, Ha SM, Ko DY, et al. Phacomatosis pigmentovascularis Ib with left-sided hemihypertrophy, interdigital gaps and scoliosis: A unique case of phacomatosis pigmentovascularis. *J Dermatol* 2013;40(1):78–9.
 138. Fernández-Guarino M, Boixeda P, de Las Heras E, et al. Phacomatosis pigmentovascularis: Clinical findings in 15 patients and review of the literature. *J Am Acad Dermatol* 2008;58(1):88–93.
 139. Happle R, Hoffmann R, Restano L, et al. Phacomatosis pigmentokeratotic: a melanocytic-epidermal twin nevus syndrome. *Am J Med Genet* 1996;65(4):363–5.
 140. Tadini G, Restano L, Gonz  les-P  rez R, et al. Phacomatosis pigmentokeratotic: report of new cases and further delineation of the syndrome. *Arch Dermatol* 1998;134(3):333–7.
 141. Mart  nez-Mench  n T, Mahiques Santos L, Vilata Corell JJ, et al. Phacomatosis pigmentokeratotic: a 20-year follow-up with malignant degeneration of both nevus components. *Pediatr Dermatol* 2005;22(1):44–7.
 142. Itin PH, Lautenschlager S, Meyer R, et al. Natural history of the Naegeli–Franceschetti–Jadassohn syndrome and further delineation of its clinical manifestations. *J Am Acad Dermatol* 1993;28(6):942–50.
 143. Lugassy J, Itin P, Ishida-Yamamoto A, et al. Naegeli–Franceschetti–Jadassohn syndrome and dermatopathia pigmentosa reticularis: two allelic ectodermal dysplasias caused by dominant mutations in KRT14. *Am J Hum Genet* 2006;79(4):724–30.
 144. Gibbs RC. Unusual striped hyperpigmentation of the torso. A sequel of abnormalities of epitrachial exfoliation. *Arch Dermatol* 1967; 95(4):385–6.
 145. Zhu YI, Fitzpatrick JE, Weston WL. Congenital curvilinear palpable hyperpigmentation. *J Am Acad Dermatol* 2005;53(2 Suppl. 1):S162–4.
 146. Berk DR, Bayliss SJ. Sock-line bands: presentation of additional follow-up and eight new cases. *Pediatr Dermatol* 2011;28:83–4.
 147. Berk DR, Bayliss SJ. Sock-line bands in infancy. *Br J Dermatol* 2007;157:1063–4.
 148. Berk DR, Bayliss SJ. Mitten-line hyperpigmentation: a reactive process analogous to sock-line hyperpigmentation. *Pediatr Dermatol* 2010;27(4):401–2.
 149. Kraemer KH. Xeroderma pigmentosum knockout mice: an immunologic tale. *J Invest Dermatol* 1996;107:291–2.
 150. Robbins JH, Kraemer KH, Lutzner MA, et al. Xeroderma pigmentosum. An inherited disease with sun sensitivity, multiple cutaneous neoplasms, and abnormal DNA repair. *Ann Intern Med* 1974;80(2):221–48.
 151. Robbins JH, Moshell AN. DNA repair processes protect human beings from premature solar skin damage: evidence from studies on xeroderma pigmentosum. *J Invest Dermatol* 1979;73(1):102–7.
 152. Robbins JH. Xeroderma pigmentosum. Defective DNA repair causes skin cancer and neurodegeneration. *JAMA* 1988;260:384–8.
 153. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. *Arch Dermatol* 1987;123:241–50.
 154. Masinjala H, Arnbj  rnsson E. Two children with xeroderma pigmentosum developing two different types of malignancies simultaneously. *Pediatr Surg Int* 1998;13:299–300.
 155. Bradford PT, Goldstein AM, Tamura D, et al. Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair. *J Med Genet* 2011;48(3):168–76.
 156. Mimaki T, Itoh N, Abe J, et al. Neurological manifestations in xeroderma pigmentosum. *Ann Neurol* 1986;20(1):70–5.
 157. Takebe H, Miki Y, Kozuka T, et al. DNA repair characteristics and skin cancers of xeroderma pigmentosum patients in Japan. *Cancer Res* 1977;37(2):490–5.
 158. Giannotti B, Vanzi L, Difonzo EM, et al. The treatment of basal cell carcinomas in a patient with xeroderma pigmentosum with a combination of imiquimod 5% cream and oral acitretin. *Clin Exp Dermatol* 2003;28(Suppl. 1):33–5.
 159. Kraemer KH, DiGiovanna JJ, Moshell AN, et al. Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *N Engl J Med* 1988;318:1633–7.
 160. Yarosh D, Klein J, O'Connor A, et al. Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomised study. *Xeroderma Pigmentosum Study Group. Lancet* 2001;357: 926–9.
 161. Schaffer JV, Orlov SJ. Radiation therapy for high-risk squamous cell carcinomas in patients with xeroderma pigmentosum: report of two cases and review of the literature. *Dermatology* 2011;223(2):97–103.
 162. Epstein JH. Postinflammatory hyperpigmentation. *Clin Dermatol* 1989;7:55–65.
 163. Goujon E, Beer F, Gay S, et al. Anetoderma of prematurity: an iatrogenic consequence of neonatal intensive care. *Arch Dermatol* 2010; 146(5):565–7.
 164. Ruiz-Maldonado R, Tamayo L, Fern  ndez-Diez J. Universal acquired melanosis. The carbon baby. *Arch Dermatol* 1978;114(5): 775–8.
 165. Rebora A, Parodi A. Universal inherited melanodyschromatosis: a case of melanosis universalis hereditaria? *Arch Dermatol* 1989; 125(10):1442–3.
 166. Braun-Falco O, Burg G, Selzle D, et al. [Diffuse congenital melanosis]. *Hautarzt* 1980;31(6): 324–7.
 167. Kint A, Oomen C, Geerts ML, et al. [Congenital diffuse melanosis]. *Ann Dermatol Vener  ol* 1987;114(1):11–16.
 168. Chernosky ME, Anderson DE, Chang JP, et al. Familial progressive hyperpigmentation. *Arch Dermatol* 1971;103(6):581–91.
 169. Wende GW, Baukus HH. A hitherto undescribed generalized pigmentation of the skin appearing in infancy in brother and sister. *J Cutan Dis* 1919;37:685–701.
 170. Wang ZQ, Si L, Tang Q, et al. Gain-of-function mutation of KIT ligand on melanin synthesis causes familial progressive hyperpigmentation. *Am J Hum Genet* 2009;84(5):672–7.
 171. Collins P, Barnes L, McCabe M. Poikiloderma congenitale: Case report and review of the literature. *Pediatr Dermatol* 1991;8:58–60.
 172. Jaworsky C. Connective tissue disease. In: Elder DE, Elenitas R, Johnson BL, et al, editors. *Lever's histopathology of the skin*. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 309–10.
 173. Clerkin EP, Sayegh S. Melanosis as the initial symptom of Addison's disease: a case report. *Lahey Clin Found Bull* 1967;16(1):173–6.
 174. Migeon C, Kenny EM, Kowarski A, et al. The syndrome of congenital adrenocortical unresponsiveness to ACTH. Report of six cases. *Pediatr Res* 1968;2:501–13.
 175. Moshang T Jr, Rosenfield RL, Bongiovanni AM, et al. Familial glucocorticoid insufficiency. *J Pediatr* 1973;82:821–6.
 176. Gorlin RJ, Sedano HO, Vickers RA, et al. Multiple mucosal neuromas, pheochromocytoma and medullary carcinoma of the thyroid – a syndrome. *Cancer* 1968;22(2):293–9.
 177. Digilio MC, Conti E, Sarkozy A, et al. Grouping of multiple-lentiginosities/LEOPARD and Noonan syndromes on the PTPN11 gene. *Am J Hum Genet* 2002;71:389–94.

178. Kontaridis MI, Swanson KD, David FS, et al. PTPN11 (Shp2) mutations in LEOPARD syndrome have dominant negative, not activating, effects. *J Biol Chem* 2006;281(10):6785–92.
179. Sarkozy A, Carta C, Moretti S, et al. Germline BRAF mutations in Noonan, LEOPARD, and cardiofaciocutaneous syndromes: molecular diversity and associated phenotypic spectrum. *Hum Mutat* 2009;30(4):695–702.
180. Pandit B, Sarkozy A, Pennacchio LA, et al. Gain-of-function RAF1 mutations cause Noonan and LEOPARD syndromes with hypertrophic cardiomyopathy. *Nat Genet* 2007;39(8):1007–12.
181. Digilio MC, Sarkozy A, Pacileo G, et al. PTPN11 gene mutations: linking the Gln-510Glu mutation to the 'LEOPARD syndrome phenotype'. *Eur J Pediatr* 2006;165(11):803–5.
182. Limongelli G, Pacileo G, Marino B, et al. Prevalence and clinical significance of cardiovascular abnormalities in patients with the LEOPARD syndrome. *Am J Cardiol* 2007;100(4):736–41.
183. Digilio MC, Lepri F, Baban A, et al. RASopathies: Clinical diagnosis in the first year of life. *Mol Syndromol* 2011;1(6):282–9.
184. Legius E, Schrandt-Stumpel C, Schollen E, et al. PTPN11 mutations in LEOPARD syndrome. *J Med Genet* 2002;39(8):571–4.
185. Chong WS, Klanwarin W, Giam YC. Generalized lentiginosis in two children lacking systemic associations: case report and review of the literature. *Pediatr Dermatol* 2004;21(2):139–45.
186. Li Y, Tong X, Yang J, et al. Q-switched alexandrite laser treatment of facial and labial lentiginosis associated with Peutz–Jeghers syndrome. *Photodermatol Photoimmunol Photomed* 2012;28(4):196–9.
187. Chang CJ, Nelson JS. Q-switched ruby laser treatment of mucocutaneous melanosis associated with Peutz–Jeghers syndrome. *Ann Plast Surg* 1996;36(4):394–7.
188. Remington BK, Remington TK. Treatment of facial lentiginosis in Peutz–Jeghers syndrome with an intense pulsed light source. *Dermatol Surg* 2002;28(11):1079–81.
189. Rosenblum GA. Cryotherapy of lentiginous mosaicism. *Cutis* 1985;35:543–4.
190. Atherton DJ, Pitcher DW, Wells RS, et al. A syndrome of various cutaneous pigmented lesions, myxoid neurofibromata and atrial myxoma: The NAME syndrome. *Br J Dermatol* 1980;103:421–9.
191. Rhodes A, Silverman RA, Harrist TJ, et al. The 'LAMB' syndrome. *J Am Acad Dermatol* 1984;10:72–82.
192. Carney JA, Gordon H, Carpenter PC, et al. The complex of myxomas, spotty pigmentation, and endocrine overactivity. *Medicine (Baltimore)* 1985;64:270–83.
193. Kirshcner LS, Carney JA, Pack SD, et al. Mutations of the gene encoding the protein kinase A type I-alpha regulatory subunit in patients with the Carney complex. *Nature Genet* 2000;26:89–92.
194. Stratakis C, Carney JA, Lin J, et al. Carney complex, a familial multiple neoplasia and lentiginosis syndrome. *J Clin Invest* 1996;97:699–705.
195. Docu I, Galaction-Nitelea O, Sirjita N, et al. Centofacial lentiginosis. A survey of 40 cases. *Br J Dermatol* 1976;94:39–43.
196. Micali G, Nasca MR, Innocenzi D, et al. Agminated lentiginosis: case report and review of the literature. *Pediatr Dermatol* 1994;11(3):241–5.
197. Schaffer JV, Lazova R, Bolognia JL. Partial unilateral lentiginosis with ocular involvement. *J Am Acad Dermatol* 2001;44(Suppl. 2):387–90.
198. Schaffer JV, Orlow SJ, Lazova R, et al. Speckled lentiginous nevus: within the spectrum of congenital melanocytic nevi. *Arch Dermatol* 2001;137:172–8.
199. Trattner A, Metzker A. Partial unilateral lentiginosis. *J Am Acad Dermatol* 1993;29:693–5.
200. Marchesi L, Naldi L, Di Landro A, et al. Segmental lentiginosis with 'jentigo' histologic pattern. *Am J Dermatopathol* 1992;14:323–7.
201. Hughes GS Jr, Park HK, Jones BE. Partial unilateral lentiginosis in a black patient with sickle cell anemia. *J Am Acad Dermatol* 1983;8(4):563–5.
202. McKelway JL. Lentigo: unilateral distribution; report of a case. *NY Med J* 1904;80:197–8.
203. Cappon D. A case of unilateral lentiginosis with mental deficiency. *Br J Dermatol Syph* 1948;60(11):371–4.
204. Pickering JG. Partial unilateral lentiginosis with associated developmental abnormalities. *Guys Hosp Rep* 1973;122(3–4):361–70.
205. Peutz JL. [A very remarkable case of familial polyposis of mucous membrane of intestinal tract and nasopharynx accompanied by peculiar pigmentation of skin and mucous membrane.] *Nederl Maandschr Geneesk* 1921;10:134–46.
206. Jeghers H, McKusick VA, Katz KH. Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits. *New Engl J Med* 1949;241:993–1005, 1031–6.
207. Tomlinson IP, Houlston RS. Peutz–Jeghers syndrome. *J Med Genet* 1997;34(12):1007–11.
208. Tovar JA, Eizaguirre I, Albert A, et al. Peutz–Jeghers syndrome in children: Report of two cases and review of the literature. *J Pediatr Surg* 1983;18:1–6.
209. Jenne DE, Reimann H, Nezu J, et al. Peutz–Jeghers syndrome is caused by mutations in a novel serine threonine kinase. *Nat Genet* 1998;18(1):38–43.
210. Hemminki A, Markie D, Tomlinson I, et al. A serine/threonine kinase gene defective in Peutz–Jeghers syndrome. *Nature* 1998;391(6663):184–7.
211. Blumenthal GM, Dennis PA. PTEN hamartoma tumor syndromes. *Europ J Hum Genet* 2008;16:1289–300.
212. Tan MH, Mester J, Peterson C, et al. A clinical scoring system for selection of patients for PTEN mutation testing is proposed on the basis of a prospective study of 3042 probands. *Am J Hum Genet* 2011;88(1):42–56.
213. Hobert JA, Eng C. PTEN hamartoma tumor syndrome: an overview. *Genet Med* 2009;11(10):687–94.
214. Fargnoli MC, Orlow SJ, Semel-Concepcion J, et al. Clinicopathologic findings in the Bannayan–Riley–Ruvalcaba syndrome. *Arch Dermatol* 1996;132(10):1214–18.
215. Gorlin RJ, Cohen MM Jr, Condon LM, et al. Bannayan–Riley–Ruvalcaba syndrome. *Am J Med Genet* 1992;44(3):307–14.
216. DiLiberti JH, Weleber RG, Budden S. Ruvalcaba–Myhre–Smith syndrome: a case with probable autosomal-dominant inheritance and additional manifestations. *Am J Med Genet* 1983;15(3):491–5.
217. Gretzula JC, Hevia O, Schachner LS, et al. Ruvalcaba–Myhre–Smith syndrome. *Pediatr Dermatol* 1988;5(1):28–32.
218. DiLiberti JH, D'Agostino AN, Ruvalcaba RH, et al. A new lipid storage myopathy observed in individuals with the Ruvalcaba–Myhre–Smith syndrome. *Am J Med Genet* 1984;18(1):163–7.
219. DiLiberti JH. Correlation of skeletal muscle biopsy with phenotype in the familial macrocephaly syndromes. *J Med Genet* 1992;29(1):46–9.
220. Urabe K, Hori Y. Dyschromatosis. *Semin Cutan Med Surg* 1997;16:81–5.
221. Miyamura Y, Suzuki T, Kono M, et al. Mutations of the RNA-specific adenosine deaminase gene (DSRAD) are involved in dyschromatosis symmetrica hereditaria. *Am J Hum Genet* 2003;73(3):693–9.
222. Zhang XJ, Gao M, Li M, et al. Identification of a locus for dyschromatosis symmetrica hereditaria at chromosome 1q11–1q21. *J Invest Dermatol* 2003;120(5):776–80.
223. Rycroft RJ, Calnan CD, Wells RS. Universal dyschromatosis, small stature and high-tone deafness. *Clin Exp Dermatol* 1977;2(1):45–8.
224. Foldès C, Wallach D, Launay JM, et al. Congenital dyschromia with erythrocyte, platelet, and erythrocyte metabolism abnormalities. *J Am Acad Dermatol* 1988;19(4):642–55.
225. Sermanowitz VJ, Krivo JM. Pigmentary demarcation lines. Comparison of Negroes with Japanese. *Br J Dermatol* 1975;93:371–7.
226. Fitcher PH. A peculiarity of pigmentation of the upper arm of Negroes. *Science* 1938;88(2294):570–1.
227. Vollum DI. Skin markings in negro children from the West Indies. *Br J Dermatol* 1972;86(3):260–3.
228. Kisch B, Nasuhoglu A. A mediasternal depigmentation line in Negroes. *Exp Med Surg* 1953;11(4):265–7.
229. Sermanowitz VJ, Krivo JM. Hypopigmented markings in Negroes. *Int J Dermatol* 1973;12(4):229–35.
230. Grimes PE, Stockton T. Pigmentary disorders in blacks. *Dermatol Clin* 1988;6:271–81.
231. Walton RG, Jacobs AH, Cox AJ. Pigmented lesions in newborn infants. *Br J Dermatol* 1976;95:389–96.
232. Alper JC, Holmes LB. The incidence and significance of birthmarks in a cohort of 4,641 newborns. *Pediatr Dermatol* 1983;1(1):58–68.
233. Osburn K, Schosser RH, Everett MA. Congenital pigmented and vascular lesions in newborn infants. *J Am Acad Dermatol* 1987;16:788–92.
234. Lorenz S, Maier C, Segerer H, et al. [Skin changes in newborn infants in the first 5 days of life]. *Hautarzt* 2000;51:396–400.
235. Boccardi D, Menni S, Ferraroni M, et al. Birthmarks and transient skin lesions in newborns and their relationship to maternal factors: a preliminary report from northern Italy. *Dermatology* 2007;215:53–8.
236. Kopf AW, Levine LJ, Rigel DS, et al. Prevalence of congenital-nevus-like nevi, nevi spili, and café au lait spots. *Arch Dermatol* 1985;121:766–9.
237. Kopf AW, Bart RS, Hennessey P. Congenital nevocytic nevi and malignant melanomas. *J Am Acad Dermatol* 1979;1:123–30.
238. Ruiz-Maldonado R. Measuring congenital melanocytic nevi. *Pediatr Dermatol* 2004;21:178–9.
239. Rhodes A, Albert LS, Weinstock MA. Congenital nevomelanocytic nevi: proportionate area expansion during infancy and early childhood. *J Am Acad Dermatol* 1996;34:51–62.

240. Changchien L, Dusza SW, Agero AL, et al. Age- and site-specific variation in the dermoscopic patterns of congenital melanocytic nevi: an aid to accurate classification and assessment of melanocytic nevi. *Arch Dermatol* 2007;143:1007–14.
241. Mark GJ, Mihm MC, Liteplo MG, et al. Congenital melanocytic nevi of the small and garment type. Clinical, histologic, and ultrastructural studies. *Hum Pathol* 1973;4:395–418.
242. Barnhill RL, Flotte TJ, Fleischli M, et al. Cutaneous melanoma and atypical Spitz tumors in childhood. *Cancer* 1995;76(10):1833–45.
243. de Wijn RS, Zaal LH, Hennekam RC, et al. Familial clustering of giant congenital melanocytic nevi. *J Plast Reconstr Aesthet Surg* 2010;63:906–13.
244. Danarti R, König A, Happel R. Large congenital melanocytic nevi may reflect paradominant inheritance implying allelic loss. *Eur J Dermatol* 2003;13:430–2.
245. Ruiz-Maldonado R, Tamayo L, Laterza AM, et al. Giant pigmented nevi: Clinical, histopathologic, and therapeutic considerations. *J Pediatr* 1992;120:906–11.
246. Egan CL, Oliveria SA, Elenitsas R, et al. Cutaneous melanoma risk and phenotypic changes in large congenital nevi: a follow-up study of 46 patients. *J Am Acad Dermatol* 1998;39:923–32.
247. Hale EK, Stein J, Ben-Porat L, et al. Association of melanoma and neurocutaneous melanocytosis with large congenital melanocytic nevi – results from the NYU-LCMN registry. *Br J Dermatol* 2005;152:512–17.
248. Bett BJ. Large or multiple congenital melanocytic nevi: occurrence of cutaneous melanoma in 1008 persons. *J Am Acad Dermatol* 2005;52:793–7.
249. Ka VS, Dusza SW, Halpern AC, et al. The association between large congenital melanocytic nevi and cutaneous melanoma: preliminary findings from an Internet-based registry of 379 patients. *Melanoma Res* 2005;15(1):61–7.
250. Foster RD, Williams ML, Barkovich AJ, et al. Giant congenital melanocytic nevi: the significance of neurocutaneous melanosis in neurologically asymptomatic children. *Plast Reconstr Surg* 2001;107:933–41.
251. Lovett A, Maari C, Decarie JC, et al. Large congenital melanocytic nevi and neurocutaneous melanocytosis: one pediatric center's experience. *J Am Acad Dermatol* 2009;61:766–74.
252. Yun SJ, Kwon OS, Han JH, et al. Clinical characteristics and risk of melanoma development from giant congenital melanocytic nevi in Korea: a nationwide retrospective study. *Br J Dermatol* 2012;166(1):115–23.
253. Sahin S, Levin L, Kopf AW, et al. Risk of melanoma in medium-sized congenital melanocytic nevi: a follow-up study. *J Am Acad Dermatol* 1998;39:428–33.
254. Swerdlow AJ, English JS, Qiao Z. The risk of melanoma in patients with congenital nevi: A cohort study. *J Am Acad Dermatol* 1995;32:595–9.
255. Fernandes NC, Machado JL. Clinical study of the congenital melanocytic naevi in the child and adolescent. *An Bras Dermatol* 2009;84:129–35.
256. Dawson HA, Atherton DJ, Mayou B. A prospective study of congenital melanocytic naevi: progress report and evaluation after 6 years. *Br J Dermatol* 1996;134(4):617–23.
257. Kinsler VA, Birley J, Atherton DJ. Great Ormond Street Hospital for Children Registry for congenital melanocytic naevi: prospective study 1988–2007. Part 1–epidemiology, phenotype and outcomes. *Br J Dermatol* 2009;160:143–50.
258. Berg P, Lindelöf B. Congenital melanocytic naevi and cutaneous melanoma. *Melanoma Res* 2003;13:441–5.
259. Zaal LH, Mooi WJ, Klip H, et al. Risk of malignant transformation of congenital melanocytic nevi: a retrospective nationwide study from The Netherlands. *Plast Reconstr Surg* 2005;116(7):1902–9.
260. Tromberg J, Bauer B, Benvenuto-Andrade C, et al. Congenital melanocytic nevi needing treatment. *Dermatol Ther* 2005;18:136–50.
261. Gonzalez J, Palangio M, Fialkoff CN, et al. Giant congenital melanocytic nevus with a large ulceration at birth: a 5-year follow-up. *J Am Acad Dermatol* 2003;49:752–4.
262. Giam YC, Williams ML, Leboit PE, et al. Neonatal erosions and ulcerations in giant congenital melanocytic nevi. *Pediatr Dermatol* 1999;16:354–8.
263. Mancianti ML, Clark WH, Hayes FA, et al. Malignant melanoma simulants arising in congenital melanocytic nevi do not show experimental evidence for a malignant phenotype. *Am J Pathol* 1990;136:817–29.
264. Leech SN, Bell H, Leonard N, et al. Neonatal giant congenital nevi with proliferative nodules: a clinicopathologic study and literature review of neonatal melanoma. *Arch Dermatol* 2004;140:83–8.
265. Bastian BC, Xiong J, Frieden IJ, et al. Genetic changes in neoplasms arising in congenital melanocytic nevi: differences between nodular proliferations and melanomas. *Am J Pathol* 2002;161:1163–9.
266. Murphy MJ, Jen M, Chang MW, et al. Molecular diagnosis of a benign proliferative nodule developing in a congenital melanocytic nevus in a 3-month-old infant. *J Am Acad Dermatol* 2008;59:518–23.
267. Kinsler VA, Chong WK, Aylett SE, et al. Complications of congenital melanocytic naevi in children: analysis of 16 years' experience and clinical practice. *Br J Dermatol* 2008;159:907–14.
268. Strauss RM, Newton Bishop JA. Spontaneous involution of congenital melanocytic nevi of the scalp. *J Am Acad Dermatol* 2008;58:508–11.
269. Villarsa E, Baselga E, Rincon C, et al. Histologic persistence of a congenital melanocytic nevus of the scalp despite clinical involution. *J Am Acad Dermatol* 2008;59:1091–2.
270. Bouffard D, Barnhill RL, Mihm MC, et al. Very late metastasis (27 years) of cutaneous malignant melanoma arising in a halo giant congenital nevus. *Dermatology* 1994;189:162–6.
271. Epstein WL, Sagebeil R, Spitzer L, et al. Halo nevi and melanoma. *JAMA* 1973;225:373–7.
272. Grefer K, Hofmann M, Sterry W, et al. Coexistence of a congenital giant hairy nevus and extensive vitiligo. *Dermatology* 2003;207:199–201.
273. Martín JM, Jordá E, Monteagudo C, et al. Desmoplastic giant congenital nevus with progressive depigmentation. *J Am Acad Dermatol* 2007;56(Suppl. 2):S10–14.
274. Ruiz-Maldonado R, Orozco-Covarrubias L, Ridaura-Sanz C, et al. Desmoplastic hairless hypopigmented naevus: a variant of giant congenital melanocytic naevus. *Br J Dermatol* 2003;148:1253–7.
275. Marghoob AA. Congenital melanocytic nevi. Evaluation and management. *Dermatol Clin* 2002;20:607–16.
276. Krengel S, Hauschild A, Schäfer T. Melanoma risk in congenital melanocytic naevi: a systematic review. *Br J Dermatol* 2006;155:1–8.
277. Gruson LM, Orlov SJ, Schaffer JV. Phacomatosis pigmentokeratotic associated with hemihypertrophy and a rhabdomyosarcoma of the abdominal wall. *J Am Acad Dermatol* 2006;55:S16–20.
278. Marghoob AA, Dusza S, Oliveria S, et al. Number of satellite nevi as a correlate for neurocutaneous melanocytosis in patients with large congenital melanocytic nevi. *Arch Dermatol* 2004;140:171–5.
279. Agero AL, Benvenuto-Andrade C, Dusza SW, et al. Asymptomatic neurocutaneous melanocytosis in patients with large congenital melanocytic nevi: a study of cases from an Internet-based registry. *J Am Acad Dermatol* 2005;53:959–65.
280. Bett BJ. Large or multiple congenital melanocytic nevi: occurrence of neurocutaneous melanocytosis in 1008 persons. *J Am Acad Dermatol* 2006;54:767–77.
281. Barkovich AJ, Frieden IJ, Williams ML. MR of neurocutaneous melanosis. *AJNR Am J Neuroradiol* 1994;15:859–67.
282. Frieden IJ, Williams ML, Barkovich AJ. Giant congenital melanocytic nevi: Brain magnetic resonance findings in neurologically asymptomatic children. *J Am Acad Dermatol* 1994;31:423–9.
283. Marnet D, Vinchon M, Mostofi K, et al. Neurocutaneous melanosis and the Dandy-Walker complex: an uncommon but not so insignificant association. *Childs Nerv Syst* 2009;25:1533–9.
284. Schreml S, Gruendobler B, Schreml J, et al. Neurocutaneous melanosis in association with Dandy-Walker malformation: case report and literature review. *Clin Exp Dermatol* 2008;33:611–14.
285. Takano T, Morimoto M, Sakaue Y, et al. Large congenital melanocytic nevi presenting with lissencephaly with an absent corpus callosum. *Congenit Anom (Kyoto)* 2008;48:97–100.
286. Ramaswamy V, Delaney H, Haque S, et al. Spectrum of central nervous system abnormalities in neurocutaneous melanocytosis. *Dev Med Child Neurol* 2012;54:563–8.
287. Kinsler VA, Abu-Amro S, Budd P, et al. Germ-line melanocortin-1-receptor genotype is associated with severity of cutaneous phenotype in congenital melanocytic nevi: a role for MC1R in human fetal development. *J Invest Dermatol* 2012;132:2026–32.
288. Kinsler V, Shaw AC, Merks JH, et al. The face in congenital melanocytic nevus syndrome. *Am J Med Genet A* 2012;158A:1014–19.
289. Bono A, Bartoli C, Zurrida SM, et al. Let's stop worrying about pigmented skin lesions in children. *Eur J Cancer* 1994;30A:417.
290. Backman ME, Kopf AW. Iatrogenic effects of general anesthesia in children: considerations in treating large congenital nevocytic nevi. *J Dermatol Surg Oncol* 1986;12:363–7.
291. Mérigou D, Prey S, Niamba P, et al. Management of congenital nevi at a dermatologic surgical paediatric outpatient clinic: consequences of an audit survey 1990–1997. *Dermatology* 2009;218:126–33.

292. Earle SA, Marshall DM. Management of giant congenital nevi with artificial skin substitutes in children. *J Craniofac Surg* 2005;16:904–7.
293. Ferguson RE Jr, Vasconez HC. Laser treatment of congenital nevi. *J Craniofac Surg* 2005;16:908–14.
294. Morley S, Gault D. Hair removal using the long-pulsed ruby laser in children. *J Clin Laser Med Surg* 2000;18:277–80.
295. Kadonaga JN, Frieden IJ. Neurocutaneous melanosis: Definition and review of the literature. *J Am Acad Dermatol* 1991;24:747–55.
296. Schaffer JV, Chang MW, Kovich OI, et al. Pigmented plexiform neurofibroma: Distinction from a large congenital melanocytic nevus. *J Am Acad Dermatol* 2007;56:862–8.
297. Asai J, Takenaka H, Ikada S, et al. Congenital malignant melanoma: a case report. *Br J Dermatol* 2004;151:693–7.
298. Campbell WA, Storlazzi E, Vintzileos AM, et al. Fetal malignant melanoma: ultrasound presentation and review of the literature. *Obstet Gynecol* 1987;70:434–9.
299. Sigg C, Pelloni F, Schnyder UW. Frequency of congenital nevi, nevi spili and café-au-lait spots and their relation to nevus count and skin complexion in 939 children. *Dermatologica* 1990;180:118–23.
300. Schaffer JV, Orlow SJ, Lazova R, et al. Speckled lentiginous nevus – classic congenital melanocytic nevus hybrid not the result of ‘collision’. *Arch Dermatol* 2001;137:1655.
301. Vidaurri de la Cruz H, Happle R. Two distinct types of speckled lentiginous nevi characterized by macular versus papular speckles. *Dermatology* 2006;212:53–8.
302. Hanayama H, Terashi H, Hashikawa K, et al. Congenital melanocytic nevi and nevus spilus have a tendency to follow the lines of Blaschko: an examination of 200 cases. *J Dermatol* 2007;34:159–63.
303. Pritchett RM, Pritchett PS. Zosteriform speckled lentiginous nevus with giant melanosomes. *Cutis* 1982;30:329–34.
304. Altman DA, Banse L. Zosteriform speckled lentiginous nevus. *J Am Acad Dermatol* 1992;27:106–8.
305. Abecassis S, Spatz A, Cazeneuve C, et al. [Melanoma within naevus spilus: 5 cases]. *Ann Dermatol Venereol* 2006;133:323–8.
306. Stern JB, Haupt HM, Aaronson CM. Malignant melanoma in a speckled zosteriform lentiginous nevus. *Int J Dermatol* 1990;29:583–4.
307. Bolognia JL. Fatal melanoma arising in a zosteriform speckled lentiginous nevus. *Arch Dermatol* 1991;127:1240–1.
308. Wagner RF Jr, Cottle WI. In situ malignant melanoma arising in a speckled lentiginous nevus. *J Am Acad Dermatol* 1989;20:125–6.
309. Guillot B, Bessis D, Barnéon G, et al. Malignant melanoma occurring on a ‘naevus on naevus’. *Br J Dermatol* 1991;124:610–11.
310. Rhodes AR, Mihm MC Jr. Origin of cutaneous melanoma in a congenital dysplastic nevus spilus. *Arch Dermatol* 1990;126:500–5.
311. Kurban RS, Preffer FI, Sober AJ, et al. Occurrence of melanoma in ‘dysplastic’ nevus spilus: report of case and analysis by flow cytometry. *J Cutan Pathol* 1992;19:423–8.
312. Corradin MT, Zattra E, Fiorentino R, et al. Nevus spilus and melanoma: case report and review of the literature. *J Cutan Med Surg* 2010;14:85–9.
313. Danarti R, Happle R. Paradoxical inheritance of twin spotting: phacomatosis pigmentovascularis as a further possible example. *Eur J Dermatol* 2003;13(6):612.
314. Happle R. Speckled lentiginous nevus syndrome: delineation of a new distinct neurocutaneous phenotype. *Eur J Dermatol* 2002;12:133–5.
315. Vente C, Neumann C, Bertsch H, et al. Speckled lentiginous nevus syndrome: report of a further case. *Dermatology* 2004;209:228–9.
316. Weedon D, Little JH. Spindle and epithelioid cell nevi in children and adults. A review of 211 cases of the Spitz nevus. *Cancer* 1977;40(1):217–25.
317. Dal Pozzo V, Benelli C, Restano L, et al. Clinical review of 247 case records of Spitz nevus (epithelioid cell and/or spindle cell nevus). *Dermatology* 1997;194(1):20–5.
318. Ferrara G, Argenziano G, Soyer HP, et al. The spectrum of Spitz nevi: a clinicopathologic study of 83 cases. *Arch Dermatol* 2005;141(11):1381–7.
319. Akasaka T, Imamura Y, Kon S. Multiple agminated juvenile melanoma arising on a hyperpigmented macule. *J Dermatol* 1993;20(10):638–42.
320. Harvell JD, Meehan SA, LeBoit PE. Spitz’s nevi with halo reaction: a histopathologic study of 17 cases. *J Cutan Pathol* 1997;24(10):611–19.
321. Hamm H, Happle R, Bröcker EB. Multiple agminated Spitz nevi: review of the literature and report of a case with distinctive immunohistological features. *Br J Dermatol* 1987;117(4):511–22.
322. Krakowski A, Tur E, Brenner S. Multiple agminated juvenile melanoma: a case with a sunburn history, and a review. *Dermatologica* 1981;163(3):270–5.
323. Boone SL, Busam KJ, Marghoob AA, et al. Two cases of multiple Spitz nevi: correlating clinical, histologic, and fluorescence in situ hybridization findings. *Arch Dermatol* 2011;147(2):227–31.
324. Zaengle AL, Heintz P, Kamino H, et al. Congenital Spitz nevus clinically mimicking melanoma. *J Am Acad Dermatol* 2002;47(3):441–4.
325. Spitz S. Melanomas of childhood [1948]. *CA Cancer J Clin* 1991;41(1):40–51.
326. Kapur P, Selim MA, Roy LC, et al. Spitz nevi and atypical Spitz nevi/tumors: a histologic and immunohistochemical analysis. *Mod Pathol* 2005;18(2):197–204.
327. Barnhill RL, Argenyi ZB, From L, et al. Atypical Spitz nevi/tumors: lack of consensus for diagnosis, discrimination from melanoma, and prediction of outcome. *Hum Pathol* 1999;30(5):513–20.
328. Farmer ER, Gonin R, Hanna MP. Discordance in the histopathologic diagnosis of melanoma and melanocytic nevi between expert pathologists. *Hum Pathol* 1996;27(6):528–31.
329. Gelbard SN, Tripp JM, Marghoob AA, et al. Management of Spitz nevi: a survey of dermatologists in the United States. *J Am Acad Dermatol* 2002;47(2):224–30.
330. Paniago-Pereira C, Maize JC, Ackerman AB. Nevus of large spindle and/or epithelioid cells (Spitz’s nevus). *Arch Dermatol* 1978;114(12):1811–23.
331. Shapiro PE. Spitz nevi. *J Am Acad Dermatol* 1993;29(4):667–8.
332. Bastian BC, LeBoit PE, Pinkel D. Mutations and copy number increase of HRAS in Spitz nevi with distinctive histopathological features. *Am J Pathol* 2000;157(3):967–72.

Acneiform and Sweat Gland Disorders

ANDREA L. ZAENGLEIN

Acneiform disorders

NEONATAL ACNE (NEONATAL CEPHALIC PUSTULOSIS)

Neonatal acne (acne neonatorum) is a very common newborn eruption, occurring in up to 20% of healthy babies. Lesions are not present at birth but typically appear within the first 2–3 weeks of life and generally improve by about 4 months of age. Small inflammatory red-pink papules and pustules predominate, occurring symmetrically on the cheeks (Fig. 25.1). The forehead, chin, eyelids, scalp, neck, back and chest can be affected as well (Fig. 25.2). Open comedones and nodules are rarely evident, and if present, suggest the possibility of true acne vulgaris, which should be treated according to infantile acne recommendations (see below).

The diagnosis of neonatal acne is usually made clinically. Giemsa staining of pustule contents reveals neutrophils and variable yeast spores. The term ‘neonatal cephalic pustulosis’ (NCP) was proposed to help differentiate this common neonatal eruption from true acne.^{1,2} In contrast to the androgen-driven infantile acne vulgaris, the pathogenesis of neonatal acne is unclear. Increased sebum and the presence of yeast flora have been implicated as possible triggers. It is known that newborn sebum excretion rates correlate with maternal sebum excretion rates perinatally and these levels subsequently decrease over the next several weeks.³ This suggests that both mother and baby are subject to the same hormonal stimulus following birth. Along with these changes, the baby begins to undergo colonization of normal flora. *Malassezia furfur*, *M. sympodialis* and other species frequently colonize neonatal skin, with prevalence rates of 35–50% at 1 week of age and increasing with age, peaking at around 90% by 3–6 months of age.⁴ However, *Malassezia* species are not uniformly cultured from the pustules of neonatal acne nor does the degree of colonization appear to correlate with severity of the clinical findings.⁵ Hence, the role of yeast in the pathogenesis of neonatal acne remains controversial.

The differential diagnosis of acneiform lesions in the neonatal and infantile period is broad (Box 25.1). More florid cases of neonatal acne are sometimes indistinguishable from seborrheic dermatitis, very early onset atopic dermatitis, miliaria rubra and in rare instances, congenital candidiasis. In atypical cases, serial follow-up and close scrutiny for lesions on other body sites is recommended. The condition is self-limited and treatment is rarely required. However, in pronounced cases, topical imidazoles, such as clotrimazole or ketoconazole cream, or a low potency topical corticosteroid, such as hydrocortisone 1% cream, may be helpful in accelerating resolution.

INFANTILE ACNE VULGARIS

In contrast to neonatal ‘acne’ – a very common condition – infantile acne vulgaris is relatively uncommon. The age of onset is usually between 6 and 12 months, with most cases resolving by 1–3 years.⁶ Boys are more commonly affected than girls.^{6–8} Clinically, it is characterized by classic acne lesions occurring primarily on the cheeks. An admixture of open and closed comedones, alone or with inflammatory papules, pustules and small nodules are seen (Figs. 25.3, 25.4). Severe forms with deep, suppurative nodules have been reported.⁹

The pathogenesis of infantile acne centers on a physiologic increased production of adrenal and gonadal androgens intrinsic to this stage of development. During the first 6–12 months of life, infant boys have elevated levels of luteinizing hormone with a resultant increased production of testosterone.¹⁰ In addition, the infantile adrenal gland, in both boys and girls, is still immature with an enlarged zona reticularis that produces elevated levels of dehydroepiandrosterone (DHEA). DHEA is subsequently converted by the sebaceous gland into more potent, acne-promoting androgens, like dihydrotestosterone.¹¹ By 12 months, adrenal androgen levels typically decrease, remaining low until the onset of adrenarche. Testicular androgen production is also minimal throughout childhood.¹² It is important to note that the majority of affected babies do not have an overt pathologic cause of hyperandrogenism and laboratory workup is usually unnecessary.⁶ However, a complete hormonal evaluation is indicated in any infant with acne that is unusually severe, persistent, or if the child has other signs of hyperandrogenism or precocious puberty, such as breast development, testicular hypertrophy, penile or clitoral enlargement, or the presence of axillary or pubic hair. Causes of infantile hyperandrogenism are listed in Box 25.2. The role of genetics in infantile acne is undoubtedly strong with 25–50% of patients reporting a positive family history of severe adolescent acne and 25% noting a sibling with infantile acne.^{6,7} Most cases of infantile acne resolve by 2–3 years of age, though in some cases, it can last up to age 5 years.¹³

It is important to treat even mild cases of infantile acne because scarring is fairly common in this age group. Up to 50% of infants with acne develop resultant pitted scars on their cheeks (Fig. 25.5).⁷ Treatment with a mild retinoid, such as adapalene 1% gel or tretinoin 0.025% cream, may be used daily with a benzoyl peroxide 2.5% cream. Certain formulations such as washes and alcohol based gels should be avoided in infants due to risk of irritating the eyes and skin. For more severe inflammatory lesions, oral erythromycin, azithromycin or trimethoprim-sulfamethoxazole (in infants 2 months and older) can be used. For the very rare cases of severe nodular



Figure 25.1 Neonatal acne. Numerous inflamed papules and pustules are localized to the forehead, eyelids and cheeks of a newborn girl.

acne, use of oral isotretinoin is effective.¹⁴ As with other forms of acne, treatment for several months is often needed, with gradual tapering of medications as the condition improves.

DRUG-INDUCED ACNE

Acne and acne-like lesions have been reported from the use of several medications. Most notably, high dose systemic corticosteroids can cause an acneiform eruption in childhood. The lesions are characteristically monomorphic pink-red papules and pustules erupting on the face, chest, shoulders and upper back. Chloracne, most commonly reported due to industrial or incidental exposure to the toxic hydrocarbon, dioxin, can also cause acne in infants and children.¹⁵ Open comedones and small nodules predominate, often involving the malar region and ears, extending to involve the nape of the neck. The central face is spared. Other potential causes of medication-induced acne are listed in [Box 25.1](#).

ACNE ASSOCIATED WITH APERT SYNDROME

Apert syndrome, or acrocephalosyndactyly, is characterized by craniosynostoses, midface hypoplasia and symmetric syndactyly of the bones of the hands and feet. Defects in skin, skeleton, brain, and visceral organs are commonly associated. Most cases are sporadic, but autosomal dominant and mosaic forms are reported. Apert syndrome is caused by a missense mutation in the fibroblast growth factor receptor-2 (*FGFR2*) gene that encodes the FGFR2 protein. Interestingly, somatic mutations in the *FGFR2* gene have been found in several cases of mosaic nevus comedonicus (acneiform unilateral nevus).¹⁶ This growth factor protein is vital for numerous cell processes including cell division, growth regulation and maturation, formation of blood vessels, wound healing, embryonic development and malignancy. Patients with Apert syndrome develop pronounced seborrhea with atypical acne lesions, involving the forearms, buttocks and thighs early in puberty, but to date this has not been described in early infancy.¹⁷ The acneiform lesions are

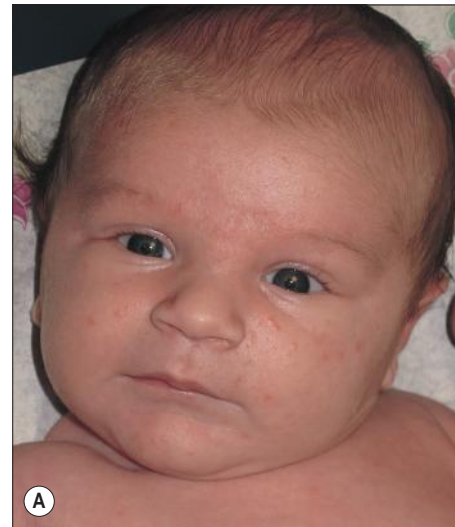


Figure 25.2 Neonatal acne. Small inflammatory papules and pustules are distributed on (A) the cheeks, forehead, and chin as well as (B) the upper back and shoulders in a 5-week-old boy.

notably resistant to standard acne treatments and isotretinoin is often required to control the process.¹⁸

HYPER-IgE SYNDROME

More than 80% of patients with autosomal dominant hyper-IgE syndrome (AD-HIES, Job syndrome) report a neonatal papulopustular eruption, most often affecting the face and scalp.^{19–21} Approximately 24% of babies with autosomal recessive hyper-IgE syndrome (AR-HIES) also have a similar indistinguishable eruption.²² The rash usually appears before 2 months of age, with the majority of cases occurring at or within the first 2 weeks after birth. The predominant lesions are crusted papules and small pustules that will wax and wane in severity. Pruritus is a common feature. The rash is associated with peripheral eosinophilia, elevated IgE levels and variable leukocytosis.¹⁹ By age 18 months, most affected infants also develop a generalized

BOX 25.1 ACNEIFORM DISORDERS IN NEONATES AND INFANTS**COMMON INFLAMMATORY DISORDERS**

- Neonatal acne (neonatal cephalic pustulosis)
- Infantile acne
- Periorificial dermatitis
- Childhood rosacea
- Milia
- Sebaceous hyperplasia
- Miliaria
- Keratosis pilaris
- Pseudoacne of the nasal crease
- Seborrheic dermatitis

UNCOMMON INFLAMMATORY DISORDERS

- Disseminated congenital comedones
- Eosinophilic folliculitis
- Behçet disease
- Acneiform follicular mucinosis

NEOPLASTIC DISORDERS

- Steatocystoma multiplex
- Eruptive vellus hair cysts

INFECTIOUS

- Trichodysplasia spinulosa
- Demodicosis
- Molluscum contagiosum

GENETIC DISORDERS

- Pustular leukemoid reaction in Down syndrome
- Patau syndrome
- SAPHO syndrome
- PAPA syndrome
- Hyper-IgE syndrome
- Lipoid proteinosis
- Apert syndrome

DRUG/TOXIN-ASSOCIATED ACNE

- Corticosteroids
- Bromides
- Cyclosporine
- Iodides
- Chloracne (dioxin)
- Vitamins B₁, B₆, B₁₂, and D₂
- Phenobarbital
- Phenytoin
- Propylthiouracil
- Disulfiram
- Quinidine
- Lithium
- Isoniazid
- Epidermal growth factor receptor inhibitors
- Anabolic steroids
- Azathioprine

xerotic, papular and follicular eczematous dermatitis concentrated on the upper body. A classic atopic dermatitis pattern is seen more frequently in AR-HIES (see [Chapter 15](#)).²¹ The eczematous rash may be secondarily impetiginized by *Staphylococcus aureus* and recurrent abscesses are typical. Over time, a pattern of recurrent infections begins to develop. Affected children develop recurrent bacterial pneumonia, commonly caused by *S. aureus*, *Streptococcus pneumoniae* or *Haemophilus influenzae*. Opportunistic organisms, such as *Pneumocystis jiroveci* and secondary fungal infections can also occur, leading to significant morbidity.²³ Chronic candidal infections of the oral mucosa, nails, and gastrointestinal tract are also described. Recurrent and resistant cutaneous viral infections, including



Figure 25.3 Infantile acne. A 6-month-old boy presents with several open comedones and a few inflamed papules across the cheeks bilaterally.



Figure 25.4 Infantile acne. Numerous inflamed papules and small nodules populate the cheeks and chin of this 5-month-old boy.

herpes simplex virus, varicella zoster virus, human papilloma-virus, and molluscum contagiosum, characterize AR-HIES and are uncommon features of the autosomal dominant form of the disease.²¹ Additionally, cutaneous malignancy, developing early in adulthood is seen almost exclusively in AR-HIES.²¹ Later in childhood, other defining features of AD-HIES become evident. These include a characteristic facies (defined by a coarse texture to the facial skin, a broad nasal bridge and a bulky nasal tip), retention of primary teeth, hyperextensibility of the joints, tortuous medium-sized blood vessels, osteopenia and bone fractures.

Histopathologic evaluation of the facial skin eruption is nonspecific but may show eosinophilic spongiotic dermatitis or eosinophilic folliculitis. Laboratory investigations reveal a nonspecific leukocytosis with eosinophilia. Despite the name

BOX 25.2 CAUSES OF HYPERANDROGENISM IN NEONATES AND INFANTS

- Cushing syndrome
- Apert syndrome
- Congenital adrenal hyperplasia (21-hydroxylase deficiency)
- Premature adrenarche
- Gonadal/adrenal tumors
- Central precocious puberty
- Male-limited precocious puberty
- Aromatase deficiency
- Hypothyroidism
- McCune–Albright syndrome
- Carney complex
- Cortisone reductase deficiency-1
- DiGeorge syndrome
- Velocardiofacial syndrome
- Aspartylglucosaminuria
- Spondyloepimetaphyseal dysplasia, Pakistani-type
- Müllerian aplasia and hyperandrogenism
- Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA)
- Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO)



Figure 25.5 Infantile acne. This 6-month-old infant was treated with topical adapalene 1% gel and benzoyl peroxide 2.5% cream daily. Note mild atrophic scarring.

‘hyper-IgE syndrome’, serum IgE levels in infancy may be only moderately elevated, indistinguishable from elevations caused by atopy. Diagnosis can be suspected because of the clinical features and confirmed with genetic testing. The differential diagnosis of the early papulopustular eruption includes common neonatal eruptions, such as neonatal acne and miliaria. As the other features of HIES develop, the differential diagnosis expands to include eczematous rashes in association with recurrent infections, including severe atopic dermatitis, tyrosine kinase 2 deficiency (hyper-IgE syndrome with atypical mycobacteriosis), Wiskott–Aldrich syndrome, Netherton syndrome, Omenn syndrome and other causes of neonatal erythroderma (see [Chapter 18](#)).

The autosomal dominant form of hyper-IgE syndrome is due to mutations in the *STAT3* gene, with the majority of cases resulting from de novo mutations in the gene. The autosomal recessive form is due to mutations in the *DOCK8* gene.



Figure 25.6 Pseudoacne of the nasal crease. Comedones and milia line up along the transverse nasal crease.

Management of hyper-IgE syndrome is aimed at prevention and directed treatment of infections as well as typical skin therapy for atopic dermatitis. Treatment with topical corticosteroids, antifungal creams and oral antibiotics are variably effective.

PSEUDOACNE OF THE NASAL CREASE

The transverse nasal crease is a horizontal anatomical demarcation line between the alar cartilage and the triangular cartilage at the lower-third of the nose. Transverse nasal crease can be familial and seen more commonly in atopic patients associated with an ‘allergic salute’.²⁴ Within this developmental fault line, milia, cysts and comedones can form ([Fig. 25.6](#)).²⁵ When lesions rupture or are traumatized, inflammatory papules result. The histology of these lesions reveal foreign body granulomatous inflammation.²⁶ This entity is primarily seen in school-age children (4–12 years of age) prior to the onset of puberty, but may be seen earlier, with resolution occurring within months to years.²⁶ Treatment of open comedones consists of surgical expression as needed. Topical retinoids and benzoyl peroxide have been used with variable results.

CHILDHOOD FLEXURAL COMEDONES

In childhood flexural comedones, noninflamed, open comedones are noted bilaterally or unilaterally in the axilla.²⁷ The groin, neck and antecubital fossa are less commonly involved. The lesions appear in early childhood with one congenital case described. Males and females are equally affected.²⁷ Several of the reported patients had associated molluscum contagiosum infection.²⁷ The lesions do not follow any segmental or Blaschkoid pattern as seen with nevus comedonicus.²⁸ Some authors suggest that childhood flexural comedones could be related to hidradenitis suppurativa.²⁷

IDIOPATHIC FACIAL ASEPTIC GRANULOMA

Idiopathic facial aseptic granuloma (IFAG; also known as ‘*pyodermite froide du visage*’) is characterized by one or more persistent, asymptomatic, inflammatory nodules most often located on the cheek. Lesions are typically red to purple and soft to slightly rubbery. The lesion size varies, with a mean diameter of 10 mm (range 3–25 mm) ([Fig. 25.7](#)). Most patients have only

TABLE
25.1

Differential diagnosis of a nodule on the face of newborns and infants

Inflammatory	Infectious	Neoplastic	Congenital anomalies
Infantile acne Folliculitis Idiopathic facial aseptic granuloma	Molluscum Botryomycosis Cat-scratch disease Sporotrichosis Cutaneous leishmaniasis Dental sinus/abscess Onchocercoma	Infantile hemangioma Pilomatricoma Pyogenic granuloma Nevus sebaceus/nevus comedonicus Mastocytoma Atypical Spitz tumor Juvenile xanthogranuloma Langerhans' cell histiocytoma Subepidermal calcified nodule Subcutaneous panniculitis-like T-cell lymphoma Rhabdomyosarcoma	Lymphangioma Nasal glioma Venous malformation Arteriovenous malformation Encephalocele Dermoid cyst



Figure 25.7 Idiopathic facial aseptic granuloma. A prominent inflamed red nodule on the cheek of a toddler. Note the eyelid involvement, which has been described in some cases. (Courtesy of Antonio Torrello, MD.)

a solitary lesion, however some have two or three. While most involve the mid-cheek, other sites including the lateral cheek infraorbital skin, or eyelids can be involved.²⁹ While the etiology is unknown, the association with concomitant eyelid chalazia has led some authors to speculate whether this entity is a variant of granulomatous rosacea.^{30,31,32}

Histopathologic evaluation reveals chronic granulomatous inflammation comprised of lymphocytes, histiocytes, neutrophils and many foreign body type giant cells. No shadow cells, cyst walls or calcium deposition should be evident. Cultures for bacteria, fungus and mycobacteria are negative, although a few reported cases were deemed secondarily positive to *Staphylococcus aureus*, *Streptococcus* species and *Enterococcus faecalis*.²⁹ Ultrasonography shows a well-demarcated, hypoechoic dermal nodule without calcification.

The differential diagnosis includes infantile acne, folliculitis, atypical Spitz tumor, resolving infantile hemangioma, pilomatricoma, and pyogenic granuloma. Infectious etiologies should also be considered, including botryomycosis, cat-scratch disease, sporotrichosis and cutaneous leishmaniasis. Table 25.1 details an expanded differential diagnosis of nodular lesions on the face of a young child.

Treatment of IFAG is often unnecessary as the lesions can resolve spontaneously, though this may take many months. Macrolide antibiotics (azithromycin, erythromycin and clarithromycin) have been used for 2 weeks to 2 months with variable improvement. Topical metronidazole cream has also been

used. In persistent cases, incision and drainage or surgical excision can be performed.²⁹

CHILDHOOD ROSACEA

Childhood rosacea is thought to be rare in young children; however, several authors argue that it is more common than generally appreciated because other relatively common childhood conditions such as perioral dermatitis (as well as IFAG) are actually variants of rosacea.^{30–33}

Childhood rosacea is observed more commonly in females with an average age of 4.2 years.³³ It has been reported in infants as young as 1 year of age.³³ A family history of rosacea is reported in 15% of patients with ocular rosacea.³⁴ Four subtypes are described: papulopustular, telangiectatic, granulomatous and ocular. Children diagnosed with rosacea typically present with a combination of ocular and cutaneous symptoms similar to the findings in adult rosacea. The papulopustular variant is most common with small, erythematous inflamed papules and pustules noted in a malar distribution (see Fig. 25.9). Telangiectasia and macular erythema with or without flushing are common. Ocular manifestations include blepharitis with meibomian gland inflammation and recurrent chalazia, hyperemia, photophobia, episcleritis, or keratoconjunctivitis, and rarely corneal ulceration.^{33,35} The presence of childhood chalazion (stye) is associated with a higher prevalence of rosacea in adulthood.³⁶

Childhood rosacea is a clinical diagnosis and biopsy is rarely indicated. The differential diagnosis is that of other infantile papulopustular eruptions. Notably, while *Demodex* mites can be associated with adult rosacea, their presence has not been documented in the childhood form.³³ Treatment of rosacea in infants consists of topical metronidazole, azelaic acid, or niacinamide. In refractory or extensive cases, oral erythromycin or azithromycin may also be employed. For ocular symptoms, systemic erythromycin or azithromycin is often used in conjunction with topical ocular erythromycin or metronidazole ophthalmic gel, ocular steroid preparations and diligent eyelid hygiene.^{33,34}

PERIORIFICAL DERMATITIS

Periorificial dermatitis is an acneiform eruption that commonly occurs in infants and young children. There is slight female predominance. The rash is characterized by small inflammatory papules and pustules grouped around the mouth, nose and eyes (Figs. 25.8, 25.9). The lesions can meld into scaling patches or



Figure 25.8 Periorificial dermatitis. Numerous small inflammatory papules localized around the mouth.



Figure 25.10 Granulomatous periorificial dermatitis. Larger papules coalesced into plaques around the mouth in a child using an inhaled corticosteroid mask. Switching to a steroid spacer led to resolution.



Figure 25.9 Periorificial dermatitis. Many small papules clustered around the mouth, nose and lower eyelids.

plaques and the margins around the mouth are often spared. The rash is usually asymptomatic but itching and rarely burning can be associated. The spectrum of involvement is broad and numerous terms have been used to describe this entity including perioral dermatitis, perioral or periorificial granulomatous dermatitis and facial Afro-Caribbean eruption.

Some patients have a granulomatous form of periorificial dermatitis characterized by well-formed small pink or skin-colored flattened papules and micronodules, which can become confluent into plaques with a striking perioral demarcation (Fig. 25.10). The perinasal folds and periocular skin are often affected; blepharitis and chalazion can also be seen. Extrafacial involvement has been described with more generalized presentations involving the trunk, extremities and vulvar skin.³⁷ Small pit-like scarring can ensue in severe cases.³⁷ Some experts believe periorificial dermatitis is a form of childhood rosacea.³⁸ The pathogenesis of periorificial dermatitis is unclear but several factors are thought to be contributory. Topical corticosteroids, systemic or inhaled corticosteroids, are thought to precipitate, or at least prolong, the eruption in many cases.^{39,40} Other possible associations include the use of skin moisturizers, secondary fusobacteria, and *Candida albicans*.

The diagnosis of periorificial dermatitis is made clinically, although a biopsy may be useful in atypical cases. Histologically, periorificial dermatitis can resemble rosacea with perifollicular and perivascular lymphohistiocytic infiltrate with variable

perifollicular granulomas.⁴¹ In cases of granulomatous periorificial dermatitis, the histologic appearance can mimic sarcoidosis with upper dermal and perifollicular granulomas admixed with lymphocytes.⁴²

The differential diagnosis of periorificial dermatitis includes seborrheic dermatitis, systemic lupus erythematosus, acne vulgaris, lupus miliaris disseminatus faciei, steroid-induced rosacea, and demodicosis. For granulomatous periorificial dermatitis, the differential diagnosis expands to include granulomatous rosacea, sarcoidosis, fungal or mycobacterial infection and familial juvenile systemic granulomatosis (Blau syndrome). Vulvar and perioral involvement may mimic cutaneous Crohn's disease.

A variety of treatments have been reported for use in the management of childhood periorificial dermatitis.⁴³ In mild cases associated with corticosteroid use, simply discontinuing the steroid may suffice. Alternate therapies include topical antimicrobial and anti-inflammatory agents including metronidazole cream or gel, clindamycin gel or lotion, erythromycin gel, azelaic acid cream and sodium sulfacetamide lotion. Topical pimecrolimus cream has also been used to treat periorificial dermatitis and to diminish flares from topical steroid withdrawal. Oral erythromycin or azithromycin may be added for refractory or severe cases. Topical corticosteroid use should be avoided as it tends to perpetuate the eruption. Long-standing cases may take many months to resolve and occasional, less severe flares are not uncommon.

DEMODICOSIS

Demodex (*D. folliculorum* and *D. brevis*) are commensal mites that reside in the pilosebaceous units of humans. While they are absent, or in very low numbers during early childhood, their numbers increase with age. However, increased numbers of follicular *Demodex* in childhood are noted in malignancy and malnourished states.⁴⁴ *Demodex* folliculitis has been reported primarily in immunocompromised children (e.g., acute lymphocytic leukemia, AIDS and occasionally other conditions), although cases in healthy children have been reported.^{45–49} Clinical findings of *Demodex* folliculitis include small erythematous papules and fine scale, most often located on the face, resembling periorificial dermatitis in a haphazard distribution (Fig. 25.11A). Reported cases in children have also

included cases of scalp demodicosis mimicking favus, marginal blepharitis demodicosis, *Demodex* folliculitis and perioral dermatitis or rosacea-like demodicosis.^{46,48,50,51} A diagnosis of demodicosis is made clinically but can usually be confirmed with direct microscopy of a scraping of follicular contents with either immersion oil or KOH preparation (Fig. 25.11B). There are numerous reported treatments for demodicosis. In young children, initial treatment with permethrin 5% cream, topical metronidazole 1% gel, or topical sodium sulfacetamide 10%/sulfur 5% formulation is suggested. Response is highly variable and sometimes multiple treatment modalities are needed to achieve clinical improvement.

GRANULOSIS RUBRA NASI

This very rare disorder presents with bright red erythema associated with prominent perspiration localized predominantly to the nose, with occasional involvement of the cheeks and chin. Small inflammatory papules, small clear vesicles and telangiectasia and have been described as well. It is noted that a clear



Figure 25.11 (A) Demodicosis in a 2-year-old girl on systemic treatment for Langerhans' cell histiocytosis. (B) An elongated eight-legged *Demodex* mite extracted from an acneiform papule is visualized with oil immersion microscopy.

rhinorrhea often accompanies the localized cutaneous findings.⁵² Most cases are reported in childhood, with onset as early as birth.⁵³ Familial cases have also been described as well as one report with pheochromocytoma.^{54,55} If required, treatment with intralesional botulinum toxin A can result in clinical improvement.⁵⁶

KERATOSIS PILARIS

Keratosis pilaris is a very common disorder of childhood with a prevalence of 2–20%.⁵⁷ Most cases are noted with onset in infancy or early childhood. Small, coarse, dry, follicular papules with variable erythema are symmetrically distributed most commonly on the proximal extensor surfaces of the arms and cheeks with generalized versions affecting the thighs, buttocks, distal extremities and the trunk (Fig. 25.12). A generalized, papular form of keratosis pilaris is described occurring in a subset of infants.⁵⁸ The papules are larger and widely spread over the entire extensor surfaces of the arms and legs, involving the cheeks as well. The lesions are typically asymptomatic except when inflamed. In inflammatory keratosis pilaris, pustules admixed with excoriated papules can be observed.

The etiology of keratosis pilaris is unknown. An autosomal dominant inheritance pattern is suspected as greater than 50% of those affected have a positive family history.⁵⁹ The disorder is associated with ichthyosis vulgaris and atopy; including asthma, atopic dermatitis, and allergic rhinitis.^{59,60} Additionally, it is reported to be seen with higher frequency in patients with diabetes mellitus, obesity and Down syndrome.^{61–64} Typically keratosis pilaris improves in the warmer summer months and worsens in the winter.⁵⁹ The natural history is noted to have three possible outcomes. In about one-third, the disorder improves by the late teen years. In 40%, the lesions remain stable; and in 20% the disorder worsens over time.⁵⁹

Treatments for keratosis pilaris are often ineffective and very rarely curative. Emollients alone are recommended for use in newborns and infants due to risk of irritation and potential



Figure 25.12 Keratosis pilaris. Classic follicular-based coarse, dry papules on the extensor surfaces of the arm of a toddler.

toxicity from other treatments. In older children, topical retinoids or keratolytic agents, including urea, glycolic acid, ammonium lactate and salicylic acid, can be tried. Topical corticosteroids should be used only for short periods to alleviate pruritic symptoms in inflamed lesions.

Keratosis pilaris variants

When keratosis pilaris is associated with pronounced erythema, the term *keratosis pilaris rubra* is used.⁵⁷ The redness is striking and overshadows the papular elements of the disorder. The facial distribution is often widespread, involving the lateral cheeks, eyebrows, chin and pinnae of the ears, giving a distinctly ruddy appearance. Extrafacial involvement may also be extensive, with involvement of the extensor surfaces of the arms, legs and often the chest, back, and buttocks (Fig. 25.13). No atrophy or hyperpigmentation is noted. While often having onset during infancy, keratosis pilaris rubra, unlike most other forms of keratosis pilaris, tends to persist into adolescence.

Another keratosis pilaris variant is *erythromelanos follicularis faciei et colli*.⁶⁵ This entity is characterized by prominent well-demarcated, reddish-brown pigmentation, telangiectasia, and pale follicular papules localized to the lateral cheeks often extending to the neck. Generalized involvement is not seen with this form. Adolescent onset has been reported.

Keratosis pilaris atrophicans is a group of follicular keratodermas considered a variant of keratosis pilaris. They are defined by hyperkeratotic follicular plugs with variable erythema associated with atrophic scarring.

Ulerythema ophryogenes is a keratosis pilaris variant localized to the lateral eyebrows and associated with localized alopecia. It has onset in infancy and is observed more frequently in boys.⁶⁶ The inheritance is either sporadic or autosomal dominant. *Ulerythema ophryogenes* is associated with Noonan syndrome and cardio-facial-cutaneous syndrome; as well as wooly hair, monosomy 18p, Cornelia de Lange syndrome and Rubinstein–Taybi syndrome.^{67–73}

Atrophoderma vermiculatum is characterized early on by small, rough follicular papules with minimal erythema that progress to atrophic cribriform scars occurring on the cheeks, preauricular region and forehead. Unilateral involvement has been reported.^{74,75} Onset typically occurs later in childhood than other forms, generally after 5 years of age.⁷⁶ Autosomal dominant and sporadic inheritance is suggested.⁷⁶

Several genetic associations are noted with these variants and generalized keratosis pilaris, including IFAP (ichthyosis follicularis, atrichia, photophobia) syndrome and cardio-facial-cutaneous syndrome (Figs. 25.14, 25.15). These are outlined in Table 25.2.

DISSEMINATED CONGENITAL COMEDONES AND IDIOPATHIC DISSEMINATED COMEDONES

These disorders are characterized by disseminated, hyperkeratotic, follicular-based papules with comedo-like plugging. The congenital case involves the face, trunk, and upper arms, including the flexural surfaces.⁷⁷ Slight improvement is noted at 2 years. The acquired case begins on the buttocks and spreads to involve the thighs, shoulders, and arms.⁷⁸ The lesions become notably inflamed and purulent and heal with depressed, crateriform scarring. The differential diagnosis includes widespread keratosis pilaris, perforating disorders, and familial dyskeratotic comedones.



Figure 25.13 Keratosis pilaris rubra. Coarse follicular white to red papules with prominent background erythema involving the extensor arms, legs, cheeks (A), and buttocks (B).



Figure 25.14 Prominent keratosis pilaris on the extensor surfaces of the arms and legs of a patient with cardio-facial-cutaneous syndrome.



Figure 25.15 IFAP syndrome. Keratosis pilaris-like papules are diffusely scattered on the face of an infant boy. Note associated alopecia of eyebrows and scalp.

TRICHODYSPLASIA SPINULOSA

Trichodysplasia spinulosa (also known as trichodysplasia or pilomatrix dysplasia of immunosuppression, cyclosporine-induced folliculo-dystrophy, or viral/virus-associated trichodysplasia) is a rare complication of immunosuppression characterized by spiny, exophytic follicular projections occurring over the midface and cheeks. The shoulders, arms, and legs may also be affected. An associated acneiform eruption may predate and continue in association with the spiny papules.⁷⁹ Loss of eyebrows has also been associated. It has been reported in children as young as 5 years⁷⁹ but, to date, not in infants.

Active polyomavirus has been identified in the majority of cases and is suspected as the cause.⁸⁰ The seroprevalence of polyomavirus is 5% in children 1–4 years, increasing to 48% by age 6–10.⁸¹ Various immunosuppressants and combinations have been associated including mycophenolate mofetil, methotrexate, 6-mercaptopurine, tacrolimus and cyclosporine. It has been reported in patients who underwent solid organ transplant, as well as in acute lymphoblastic leukemia. Histologically, there is abnormal follicle maturation, overgrowth of the inner root sheath epithelium and hyperkeratosis of the infundibulum. Intranuclear viral particles can be seen on electron microscopy.

Topical cidofovir 3% cream has been effective in some cases, as well as topical tazarotene 0.1% cream, and oral valganciclovir. In several cases, the lesions resolved when the immunosuppression was eventually discontinued.

Eccrine gland disorders

ECCRINE HIDRADENITIS

Several forms of neutrophilic eccrine hidradenitis (NEH) have been reported. These include childhood neutrophilic eccrine hidradenitis, palmoplantar eccrine hidradenitis, as well as chemotherapy-associated neutrophilic eccrine hidradenitis. Associations of neutrophilic eccrine hidradenitis are listed in [Table 25.3](#).



Figure 25.16 Palmoplantar eccrine hidradenitis. Tender, purplish-red nodules on the plantar surface of a 23-month-old child's feet.

Childhood neutrophilic eccrine hidradenitis

Childhood neutrophilic eccrine hidradenitis (CNEH) is an idiopathic form described in infants and toddlers.⁸² In CNEH, urticarial, red nodules and plaques are primarily localized to the arms and legs. The trunk and scalp can also be involved. Generalized forms have also been observed.⁸³ The lesions can be tender but are often asymptomatic. The typical age range of a child with CNEH varies from 6 to 14 months, with a median age of 9.1 months.⁸² It is seen almost exclusively in the hot summer months. An elevated white count is common and an increased C-reactive protein can be seen.

Histopathologic evaluation reveals a dense neutrophilic infiltrate concentrated around the ductal and secretory portions of the eccrine duct. No leukocytoclastic vasculitis is seen.

The etiology of CNEH is unknown and affected children are otherwise healthy. Coagulase-negative *Staphylococcus* was cultured in a minority of cases making its association unclear. However, the clear summertime prevalence and association with excessive heat exposure and sweating may hold a clue to its pathogenesis.⁸⁴

The differential diagnosis of CNEH includes: urticaria, erythema multiforme, miliaria, erythema nodosum, arthropod bites, papular urticaria, atypical viral exanthema, and Sweet syndrome.

Lesions typically resolve in approximately 3 weeks. Topical corticosteroids, oral corticosteroids and nonsteroidal anti-inflammatory agents have all been used to alleviate any symptoms and questionably, speed resolution.

Palmoplantar eccrine hidradenitis

Palmoplantar eccrine hidradenitis is characterized by tender, pink to red papules and nodules localized to the palms and soles ([Fig. 25.16](#)).⁸⁵ This form is typically seen in school-aged

TABLE
25.2

Genetic disorders associated with keratosis pilaris

Disorder	Inheritance	Genetic defect	Features
Bazex–Dupre–Christol syndrome	X-linked dominant	Unknown	Congenital hypotrichosis, atrophoderma vermiculatum affecting the dorsal hands and feet, face, and extensor surfaces of the elbows or knees, and the development of basal cell neoplasms in early adulthood. Extensive milia of the face in infancy and childhood.
Rombo syndrome	Autosomal dominant (?)	Unknown	Atrophoderma vermiculatum, milia, hypotrichosis, trichoeplitheliomas, basal cell carcinomas and peripheral vasodilation with cyanosis.
Keratosis follicularis spinulosa decalvans (KFSD)	X-linked	<i>MBTPS2</i> gene Allelic to IFAP syndrome	Widespread keratosis pilaris, cicatricial alopecia of the scalp, eyebrows, and eyelashes. Photophobia, blepharitis/conjunctivitis, and corneal dystrophy are variable. Female carriers exhibit milder phenotype.
Ichthyosis follicularis-atrichia-photophobia syndrome (IFAP), with or without BRESHECK syndrome	X-linked	<i>MBTPS2</i> gene Allelic to KFSD syndrome	Widespread spiny, keratotic follicular papules, sparse nonscarring alopecia of the scalp, eyebrows, and eyelashes and photophobia. May be associated with BRESHECK syndrome (brain anomalies, mental retardation, ectodermal dysplasia, skeletal malformations, Hirschsprung disease, ear/eye abnormalities, cleft palate/cryptorchidism, and kidney dysplasia.) Dry, scaling skin noted at birth.
Cardio-facio-cutaneous syndrome	Autosomal dominant Sporadic	Heterozygous gain-of-function mutations in: <i>KRAS</i> , <i>BRAF</i> , <i>MEK1</i> , or <i>MEK2</i>	Distinctive facial appearance (high forehead with bitemporal constriction, hypoplastic supraorbital ridges, downslanting palpebral fissures, a depressed nasal bridge, and posteriorly angulated ears with prominent helices), heart defects (pulmonic stenosis, atrial septal defect, and hypertrophic cardiomyopathy), and mental retardation. Associated with atrophoderma vermiculatum of the eyebrows and eyelashes, infantile hemangioma, atopic dermatitis and ichthyosis.
Noonan syndrome	Autosomal dominant Sporadic	<i>PTPN11</i> gene Allelic to LEOPARD syndrome	Distinctive facial appearance (hypertelorism, downward eyeslant, epicanthic folds and low-set posteriorly rotated ears), short stature, short neck with webbing, cardiac anomalies (pulmonic stenosis, atrial and ventricular septal defects and hypertrophic cardiomyopathy), bony abnormalities (pectus excavatum, brachydactyly) deafness, motor delay, and a bleeding diathesis. Associated with atrophoderma vermiculatum of the eyebrows and eyelashes and sparse wooly hair.
Monilethrix	Autosomal dominant	Hair cortex keratin genes: <i>KRTHB1</i> , <i>KRTHB3</i> , or <i>KRTHB6</i>	Short, broken hair. Beaded appearance on microscopy. Associated with follicular, keratotic papules on neck, extensor arms and legs and onychodystrophy.
Hereditary mucoepithelial dysplasia	Autosomal dominant	Unknown	Well-demarcated fiery red mucosa, psoriasiform perineal plaques, thin and brittle nonscarring alopecia. Other findings include follicular keratoses, cataracts and blindness.
Keratitis–ichthyosis–deafness syndrome (KID)	Autosomal dominant	<i>Connexin-26</i>	Eye involvement (keratitis, corneal erosions, photophobia, blindness), honeycomb ichthyosis and palmoplantar keratoderma, sensorineural deafness. Scant, thin hair on scalp, eyelashes, eyebrows. Increased bacterial and fungal infections.

children and adolescents and is often associated with heat, moisture and physical activity. Children as young as 4 years old have been reported.⁸⁶ Management consists of rest, elevation, and nonsteroidal anti-inflammatory agents. Lesions resolve over days to weeks, with recurrences quite common. Palmo-plantar eccrine hidradenitis typically arises within 1–2 weeks after starting chemotherapy, manifesting as painful, bright pink-red papules, nodules and plaques on the trunk, extremities, and face. Linear, annular, pustular, and purpuric forms have been reported. Generally, patients are febrile and neutropenic, secondary to the underlying malignancy.

Histopathologic examination classically reveals vacuolar degeneration within the secretory portion of the eccrine duct along with a neutrophilic infiltrate. Inflammation may be sparse, however, in severely neutropenic patients. Squamous metaplasia is sometimes seen.

Chemotherapy. NEH was originally described in association with acute myelogenous leukemia (AML) being treated with chemotherapy, particularly cytarabine; however, many other chemotherapeutic agents have subsequently been implicated. Corticosteroids and dapson can be effective in treatment. Lesions resolve shortly after discontinuation of chemotherapy.

Hyperhidrosis

Causes of hypohidrosis and hyperhidrosis are varied, including genetic and acquired disorders of the skin and nervous system. Depending on the cause, the effects can be localized or generalized. A list of disorders that result in impaired sweating are given in Tables 25.4 and 25.5.

TABLE
25.3

Associations of neutrophilic eccrine hidradenitis

Neoplastic	Infectious	Medication	Other
Acute myelogenous leukemia	<i>Serratia</i>	Cytarabine	Behçet disease
Osteosarcoma	<i>Enterobacter cloacae</i>	Bleomycin	Hemodialysis
Non-Hodgkin lymphoma	HIV	Granulocyte colony stimulating factor (GCSF)	
Hodgkin lymphoma	<i>Staphylococcus</i>	Cyclophosphamide	
Chronic lymphocytic leukemia	<i>Streptococcus</i>	5-fluorouracil	
	<i>Pseudomonas</i>	Vinca alkaloids	
	<i>Nocardia</i>	Imatinib mesylate	
		Zidovudine	
		Anthracyclines	
		Methotrexate	
		Mitoxantrone	

TABLE 25.4 Causes of hyperhidrosis in neonates and infants			
Growths/tumors	Metabolic	Genetic	Other
Localized hyperhidrosis			
Eccrine nevus Granulosa rubra nasi Blue rubber bleb nevus (venous malformation) Glomus tumor		Auriculotemporal (Frey) syndrome POEMS syndrome Pachydermoperiostosis	Processes affecting sympathetic innervations Idiopathic unilateral circumscribed hyperhidrosis
Generalized hyperhidrosis			
Thalamic storm Spinal cord injuries Intrathoracic processes	Febrile illnesses Thyrotoxicosis Diabetes mellitus Congestive heart failure	Familial dysautonomia (Riley–Day syndrome) Congenital autonomic dysfunction with universal pain loss Episodic hypothermia with hyperhidrosis	Post-traumatic hypertension Olfactory hyperhidrosis Paroxysmal unilateral hyperhidrosis Poisoning (insecticides, herbicides, mercury) Post-sympathectomy Harlequin syndrome (hemifacial flushing and contralateral hypohidrosis)

TABLE 25.5 Causes of hypohidrosis	
Generalized hypohidrosis	
GENETIC	OTHER
X-linked hypohidrotic ectodermal dysplasia	Miliaria
Autosomal recessive hypohidrotic ectodermal dysplasia	Xerosis
Autosomal dominant hypohidrotic ectodermal dysplasia	Graft-versus-host disease
Anhidrotic ectodermal dysplasia with T-cell immunodeficiency	Chronic idiopathic anhidrosis
Fabry disease	Medications (anticholinergics, botulinum toxin, clonidine, barbiturates, α2 receptor antagonists)
Bazex syndrome	Topiramate, zonisamide
Incontinentia pigmenti	
Naegeli–Franceschetti–Jadassohn syndrome	
Rapp–Hodgkin syndrome	
Limb-mammary syndrome	
Dermatopathia pigmentosa reticularis	
Riley–Day syndrome	
Ichthyoses (lamellar, congenital ichthyosiform erythroderma, epidermolytic ichthyosis)	
Congenital insensitivity to pain with anhidrosis	
Progressive segmental anhidrosis with Adie’s tonic pupils (Ross syndrome)	
Autonomic insufficiency syndrome	
Localized hypohidrosis	
OTHER	
Local damage to glands	
Harlequin syndrome (hemifacial flushing and contralateral hypohidrosis)	
Burns	
Radiation	



Figure 25.17 Harlequin syndrome. Transient unilateral flushing associated with hyperhidrosis, tearing and rhinorrhea.

of age, with the introduction of solid foods. Flushing is noted immediately within seconds of mastication and episodes last up to 1 hour.⁸⁷ Symptoms tend to improve slowly over several years. Bilateral and familial variants have been reported, likely due to congenital anomalies of the nerve.⁸⁸ Unlike in adults, gustatory sweating is not common in infancy, and cases with just flushing are described. Damage to the nerve during delivery, particularly from use of forceps, is noted in more than 50% of cases.⁸⁷ Other reported associations include buccal tumors such as plexiform neurofibroma associated with neurofibromatosis type 1,⁸⁹ congenital hemangiopericytoma⁹⁰ and as a complication of parotidectomy.

Due to the association with eating, auriculotemporal nerve syndrome is often initially confused with food allergy. The differential diagnosis also includes Harlequin syndrome.

AURICULOTEMPORAL NERVE SYNDROME (FREY SYNDROME)

This syndrome is associated with prominent unilateral facial flushing and sweating along the path of the auriculotemporal nerve. It typically appears in infancy, between 2 and 6 months

HARLEQUIN SYNDROME

Harlequin syndrome (hemifacial flushing with contralateral hypohidrosis; not to be confused with Harlequin ichthyosis and Harlequin color change) is a rare disorder of autonomic dysfunction characterized by unilateral hypohidrosis with

compensatory contralateral flushing and sweating associated with tearing and rhinorrhea (Fig. 25.17). Episodes of intense erythema defined by the midline are often triggered by heat or exercise. Neurologic and/or ocular symptoms such as Horner syndrome may be present. This syndrome may be primary (idiopathic) or secondary (due to neck tumors, vascular compromise of the cervical chain or brainstem injury). It is postulated that the syndrome could be an exaggerated response on the side opposite to the sympathetic deficit side, serving as a compensatory mechanism to maintain normal heat regulation.⁹¹

Hypohidrosis and anhidrosis

Hypohidrosis and anhidrosis are rare conditions in newborns and infants. Most genetic cases are attributable to ectodermal dysplasias, which are discussed in Chapter 29.

CONGENITAL INSENSITIVITY TO PAIN WITH ANHIDROSIS

Congenital insensitivity to pain with anhidrosis is an autosomal, recessive hereditary sensory neuropathy due to a defect in the *NTRK1* gene.⁹² Affected children will have normal numbers of sweat glands on biopsy but have markedly impaired functioning, with no clinical sweating. Fever is often the presenting symptom and uncontrolled hyperthermia can result in death. Other findings include mental retardation and self-mutilation. Traumatic lingual ulceration (Riga-Fede disease) presenting as granulomatous exophytic plaques on the lips and tongue can occur in infants with inherited insensitivities to pain.⁹³

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Table 3 is available online at [ExpertConsult.com](#)

KEY REFERENCES

6. Cunliffe WJ, Baron SE, Coulson IH. A clinical and therapeutic study of 29 patients with infantile acne. *Br J Dermatol* 2001;145(3):463–6.
12. Lucky AW. A review of infantile and pediatric acne. *Dermatology* 1998;196(1):95–7.
23. Freeman AF, Holland SM. Clinical manifestations, etiology, and pathogenesis of the hyper-IgE syndromes. *Pediatr Res* 2009;65(5 Pt 2):32R–37R.
29. Boralevi F, Léauté-Labrèze C, Lepreux S, et al. Idiopathic facial aseptic granuloma: a multicentre prospective study of 30 cases. *Br J Dermatol* 2007;156(4):705–8.
33. Chamaillard M, Mortemousque B, Boralevi F, et al. Cutaneous and ocular signs of childhood rosacea. *Arch Dermatol* 2008;144(2):167–71.
38. Nguyen V, Eichenfield LF. Periorificial dermatitis in children and adolescents. *J Am Acad Dermatol* 2006;55(5):781–5.
47. Patrizi A, Neri I, Chiericato C, et al. Demodicidosis in immunocompetent young children: report of eight cases. *Dermatology* 1997;195(3):239–42.
57. Marqueling AL, Gilliam AE, Prendiville J, et al. Keratosis pilaris rubra: a common but under-recognized condition. *Arch Dermatol* 2006;142(12):1611–16.
82. Shih IH, Huang YH, Yang CH, et al. Childhood neutrophilic eccrine hidradenitis: a clinicopathologic and immunohistochemical study of 10 patients. *J Am Acad Dermatol* 2005;52(6):963–6.
87. Dizon MV, Fischer G, Jopp-McKay A, et al. Localized facial flushing in infancy. Auriculotemporal nerve (Frey) syndrome. *Arch Dermatol* 1997;133(9):1143–5.

REFERENCES

- Bardazzi F, Patrizi A. Transient cephalic neonatal pustulosis. *Arch Dermatol* 1997;133(4):528–30.
- Rapelanoro R, Mortureux P, Couprie B, et al. Neonatal *Malassezia furfur* pustulosis. *Arch Dermatol* 1996;132(2):190–3.
- Henderson CA, Taylor J, Cunliffe WJ. Sebum excretion rates in mothers and neonates. *Br J Dermatol* 2000;142(1):110–11.
- Bernier V, Weill FX, Hirigoyen V, et al. Skin colonization by *Malassezia* species in neonates: a prospective study and relationship with neonatal cephalic pustulosis. *Arch Dermatol* 2002;138(2):215–18.
- Bergman JN, Eichenfield LF. Neonatal acne and cephalic pustulosis: is *Malassezia* the whole story? *Arch Dermatol* 2002;138(2):255–7.
- Cunliffe WJ, Baron SE, Coulson IH. A clinical and therapeutic study of 29 patients with infantile acne. *Br J Dermatol* 2001;145(3):463–6.
- Hello M, Prey S, Léauté-Labrèze C, et al. Infantile acne: a retrospective study of 16 cases. *Pediatr Dermatol* 2008;25(4):434–8.
- Katsambas AD, Katoulis AC, Stavropoulos P. Acne neonatorum: a study of 22 cases. *Int J Dermatol* 1999;38(2):128–30.
- Mengesha YM, Hansen RC. Toddler-age nodulocystic acne. *J Pediatr* 1999;134(5):644–8.
- Duke EM. Infantile acne associated with transient increases in plasma concentrations of luteinising hormone, follicle-stimulating hormone, and testosterone. *BMJ (Clin Res Ed.)* 1981;282(6272):1275–6.
- Thiboutot D, Jabara S, McAllister JM, et al. Human skin is a steroidogenic tissue: steroidogenic enzymes and cofactors are expressed in epidermis, normal sebocytes, and an immortalized sebocyte cell line (SEB-1). *J Invest Dermatol* 2003;120(6):905–14.
- Lucky AW. A review of infantile and pediatric acne. *Dermatology* 1998;196(1):95–7.
- Jansen T, Burgdorf WH, Plewig G. Pathogenesis and treatment of acne in childhood. *Pediatr Dermatol* 1997;14(1):17–21.
- Barnes CJ, Eichenfield LF, Lee J, et al. A practical approach for the use of oral isotretinoin for infantile acne. *Pediatr Dermatol* 2005;22(2):166–9.
- Caputo R, Monti M, Ermacora E, et al. Cutaneous manifestations of tetrachlorodibenzo-p-dioxin in children and adolescents. Follow-up 10 years after the Seveso, Italy, accident. *J Am Acad Dermatol* 1988;19(5 Pt 1):812–19.
- Munro CS, Wilkie AO. Epidermal mosaicism producing localised acne: somatic mutation in FGFR2. *Lancet* 1998;352(9129):704–5.
- Solomon LM, Cohen MM Jr, Pruzansky S. Pilo-sebaceous abnormalities in Apert type acrocephalosyndactyly. *Birth Defects Orig Artic Ser* 1971;7(8):193–5.
- Parker TL, Roth JG, Esterly NB. Isotretinoin for acne in Apert syndrome. *Pediatr Dermatol* 1992;9(3):298–300.
- Chamlin SL, McCalmont TH, Cunningham BB, et al. Cutaneous manifestations of hyper-IgE syndrome in infants and children. *J Pediatr* 2002;141(4):572–5.
- Olaiwan A, Chandresris MO, Fraitag S, et al. Cutaneous findings in sporadic and familial autosomal dominant hyper-IgE syndrome: a retrospective, single-center study of 21 patients diagnosed using molecular analysis. *J Am Acad Dermatol* 2011;65(6):1167–72.
- Chu EY, Freeman AF, Jing H, et al. Cutaneous manifestations of *DOCK8* deficiency syndrome. *Arch Dermatol* 2012;148(1):79–84.
- Eberting CL, Davis J, Puck JM, et al. Dermatitis and the newborn rash of hyper-IgE syndrome. *Arch Dermatol* 2004;140(9):1119–25.
- Freeman AF, Holland SM. Clinical manifestations, etiology, and pathogenesis of the hyper-IgE syndromes. *Pediatr Res* 2009;65(5 Pt 2):32R–37R.
- Del-Rio E, Pena J, Aguilar A. Milia cysts along the nasal groove in a child. *Clin Exp Dermatol* 1993;18(3):289–90.
- Shelley WB, Shelley ED, Pansky B. The transverse nasal line: an embryonic fault line. *Br J Dermatol* 1997;137(6):963–5.
- Risma KA, Lucky AW. Pseudoacne of the nasal crease: a new entity? *Pediatr Dermatol* 2004;21(4):427–31.
- Larralde M, Abad ME, Muñoz AS, et al. Childhood flexural comedones: a new entity. *Arch Dermatol* 2007;143(7):909–11.
- Cho SB, Lee SH, Jung JY, et al. A case of childhood flexural comedones. *J Eur Acad Dermatol Venereol* 2009;23(3):366–7.
- Boralevi F, Léauté-Labrèze C, Lepreux S, et al. Idiopathic facial aseptic granuloma: a multicenter prospective study of 30 cases. *Br J Dermatol* 2007;156(4):705–8.
- Neri I, Raone B, Dondi A, et al. Should idiopathic facial aseptic granuloma be considered granulomatous rosacea? Report of three pediatric cases. *Pediatr Dermatol* 2012;30(1):109–11.
- Al Dhaybi R, McCuaig C, Kokta V. A periocular nodule in a child. *Clin Exp Dermatol* 2011;36(1):105–6.
- Baroni A, Russo T, Faccenda F, et al. Idiopathic facial aseptic granuloma in a child: a possible expression of childhood rosacea. *Pediatr Dermatol* 2012;30(3):394–5.
- Chamaillard M, Mortemousque B, Boralevi F, et al. Cutaneous and ocular signs of childhood rosacea. *Arch Dermatol* 2008;144(2):167–71.
- Donaldson KE, Karp CL, Dunbar MT. Evaluation and treatment of children with ocular rosacea. *Cornea* 2007;26(1):42–6.
- Erzurum SA, Feder RS, Greenwald MJ. Acne rosacea with keratitis in childhood. *Arch Ophthalmol* 1993;111(2):228–30.
- Bamford JT, Gessert CE, Renier CM, et al. Childhood stye and adult rosacea. *J Am Acad Dermatol* 2006;55(6):951–5.
- Urbatsch AJ, Frieden I, Williams ML, et al. Extrafacial and generalized granulomatous periorificial dermatitis. *Arch Dermatol* 2002;138(10):1354–8.
- Nguyen V, Eichenfield LF. Periorificial dermatitis in children and adolescents. *J Am Acad Dermatol* 2006;55(5):781–5.
- Manders SM, Lucky AW. Perioral dermatitis in childhood. *J Am Acad Dermatol* 1992;27(5 Pt 1):688–92.
- Clementson B, Smidt AC. Periorificial dermatitis due to systemic corticosteroids in children: report of two cases. *Pediatr Dermatol* 2012;29(3):331–2.
- Henningsen E, Bygum A. Budesonide-induced periorificial dermatitis presenting as chalazion and blepharitis. *Pediatr Dermatol* 2011;28(5):596–7.
- Frieden IJ, Prose NS, Fletcher V, et al. Granulomatous perioral dermatitis in children. *Arch Dermatol* 1989;125(3):369–73.
- Wollenberg A, Bieber T, Dirschka T, et al. [Perioral dermatitis]. *J Dtsch Dermatol Ges* 2011;9(5):422–7.
- Kaya S, Selimoglu MA, Kaya OA, et al. Prevalence of *Demodex folliculorum* and *brevi* in childhood malnutrition and malignancy. *Pediatr Int* 2013;55(1):85–9.
- Damian D, Rogers M. *Demodex* infestation in a child with leukaemia: treatment with ivermectin and permethrin. *Int J Dermatol* 2003;42(9):724–6.
- Herron MD, O'Reilly MA, Vanderhooft SL. Refractory *Demodex* folliculitis in five children with acute lymphoblastic leukemia. *Pediatr Dermatol* 2005;22(5):407–11.
- Patrizi A, Neri I, Chiericato C, et al. Demodicidosis in immunocompetent young children: report of eight cases. *Dermatology* 1997;195(3):239–42.
- Morrás PG, Santos SP, Imedio IL, et al. Rosacea-like demodicidosis in an immunocompromised child. *Pediatr Dermatol* 2003;20(1):28–30.
- Sahn EE, Sheridan DM. Demodicidosis in a child with leukemia. *J Am Acad Dermatol* 1992;27(5 Pt 2):799–801.
- Garcia-Vargas A, Mayorga-Rodríguez JA, Sandoval-Tress C. Scalp demodicidosis mimicking favus in a 6-year-old boy. *J Am Acad Dermatol* 2007;57(2 Suppl):S19–21.
- Liang L, Safran S, Gao Y, et al. Ocular demodicosis as a potential cause of pediatric blepharokeratitis. *Cornea* 2010;29(12):1386–91.
- Goldsmith WN. Granulosis Rubra Nasi (Jadassohn). *Proc R Soc Med* 1932;25(4):390.
- Williams DI. Granulosis Rubra Nasi. *Proc R Soc Med* 1947;40(9):499.
- Hellier FF. Granulosis Rubra Nasi in a mother and daughter. *BMJ* 1937;2(4012):1068.
- Heid E, Samain F, Jelen G, et al. [Granulosis rubra nasi and pheochromocytoma]. *Ann Dermatol Venereol* 1996;123(2):106–8.
- Grazziotin TC, Buffon RB, da Silva Manzoni AP, et al. Treatment of granulosis rubra nasi with botulinum toxin type A. *Dermatol Surg* 2009;35(8):1298–9.
- Marqueling AL, Gilliam AE, Prendiville J, et al. Keratosis pilaris rubra: a common but underrecognized condition. *Arch Dermatol* 2006;142(12):1611–16.
- Castela E, Chiaverini C, Boralevi F, et al. Papular, profuse, and precocious keratosis pilaris. *Pediatr Dermatol* 2012;29(3):285–8.
- Poskitt L, Wilkinson JD. Natural history of keratosis pilaris. *Br J Dermatol* 1994;130(6):711–13.
- Mevorah B, Marazzi A, Frenk E. The prevalence of accentuated palmoplantar markings and keratosis pilaris in atopic dermatitis, autosomal dominant ichthyosis and control dermatological patients. *Br J Dermatol* 1985;112(6):679–85.
- Yosipovitch G, Mevorah B, Mashiach J, et al. High body mass index, dry scaly leg skin and atopic conditions are highly associated with keratosis pilaris. *Dermatology* 2000;201(1):34–6.
- Yosipovitch G, Hodak E, Vardi P, et al. The prevalence of cutaneous manifestations in IDDM patients and their association with diabetes risk factors and microvascular complications. *Diabetes Care* 1998;21(4):506–9.
- Daneshpazhoo M, Nazemi TM, Bigdeloo L, et al. Mucocutaneous findings in 100 children with

- Down syndrome. *Pediatr Dermatol* 2007;24(3):317–20.
64. Forman L. Keratosis pilaris. *Br J Dermatol* 1954;66(8–9):279–82.
 65. Andersen BL. Erythromelanos follicularis faciei et colli. Case reports. *Br J Dermatol* 1980;102(3):323–5.
 66. Davenport DD. Ulerythema ophryogenes; review and report of a case. Discussion of relationship to certain other skin disorders and association with internal abnormalities. *Arch Dermatol* 1964;89:74–80.
 67. Pierini DO, Pierini AM. Keratosis pilaris atrophicans faciei (ulerythema ophryogenes): a cutaneous marker in the Noonan syndrome. *Br J Dermatol* 1979;100(4):409–16.
 68. Siegel DH, McKenzie J, Frieden IJ, et al. Dermatological findings in 61 mutation-positive individuals with cardiofaciocutaneous syndrome. *Br J Dermatol* 2011;164(3):521–9.
 69. Armour CM, Allanson JE. Further delineation of cardio-facio-cutaneous syndrome: clinical features of 38 individuals with proven mutations. *J Med Genet* 2008;45(4):249–54.
 70. Chien AJ, Valentine MC, Sybert VP. Hereditary woolly hair and keratosis pilaris. *J Am Acad Dermatol* 2006;54(2 Suppl):S35–9.
 71. Florez A, Fernandez-Redondo V, Toribio J. Ulerythema ophryogenes in Cornelia de Lange syndrome. *Pediatr Dermatol* 2002;19(1):42–5.
 72. Nazarenko SA, Ostroverkhova NV, Vasiljeva EO, et al. Keratosis pilaris and ulerythema ophryogenes associated with an 18p deletion caused by a Y/18 translocation. *Am J Med Genet* 1999;85(2):179–82.
 73. Gómez Centeno P, Rosón E, Peteiro C, et al. Rubinstein – Taybi syndrome and ulerythema ophryogenes in a 9-year-old boy. *Pediatr Dermatol* 1999;16(2):134–6.
 74. Arrieta E, Milgram-Sternberg Y. Honeycomb atrophy on the right cheek. Folliculitis ulerythematosa reticulata (atrophoderma vermiculatum). *Arch Dermatol* 1988;124(7):1101–4.
 75. Hsu S, Nikko A. Unilateral atrophic skin lesion with features of atrophoderma vermiculatum: a variant of the epidermal nevus syndrome? *J Am Acad Dermatol* 2000;43(2 Pt 1):310–12.
 76. Frosch PJ, Brumage MR, Schuster-Pavlovic C, et al. Atrophoderma vermiculatum. Case reports and review. *J Am Acad Dermatol* 1988;18(3):538–42.
 77. Vano-Galvan S, Hernández-Martín A, Colmenero I, et al. Disseminated congenital comedones. *Pediatr Dermatol* 2011;28(1):58–9.
 78. Zhang RZ, Zhu WY. Idiopathic disseminated comedones in a child. *Pediatr Dermatol* 2006;23(2):163–6.
 79. Schwieger-Briel A, Balma-Mena A, Ngan B, et al. Trichodysplasia spinulosa – a rare complication in immunosuppressed patients. *Pediatr Dermatol* 2010;27(5):509–13.
 80. Kazem S, van der Meijden E, Kooijman S, et al. Trichodysplasia spinulosa is characterized by active polyomavirus infection. *J Clin Virol* 2012;53(3):225–30.
 81. Chen T, Mattila PS, Jartti T, et al. Seroepidemiology of the newly found trichodysplasia spinulosa-associated polyomavirus. *J Infect Dis* 2011;204(10):1523–6.
 82. Shih IH, Huang YH, Yang CH, et al. Childhood neutrophilic eccrine hidradenitis: a clinicopathologic and immunohistochemical study of 10 patients. *J Am Acad Dermatol* 2005;52(6):963–6.
 83. Andreu-Barasoain M, Calzado L, Salamanca J, et al. Generalized idiopathic neutrophilic eccrine hidradenitis in a 7-month-old child. *J Am Acad Dermatol* 2012;67(4):e133–4.
 84. Lee WJ, Kim CH, Chang SE, et al. Generalized idiopathic neutrophilic eccrine hidradenitis in childhood. *Int J Dermatol* 2010;49(1):75–8.
 85. Simon M Jr, Cremer H, von den Driesch P. Idiopathic recurrent palmoplantar hidradenitis in children. Report of 22 cases. *Arch Dermatol* 1998;134(1):76–9.
 86. Kanzaki H, Oono T, Makino E, et al. Neutrophilic eccrine hidradenitis: report of two cases. *J Dermatol* 1995;22(2):137–42.
 87. Dizon MV, Fischer G, Jopp-McKay A, et al. Localized facial flushing in infancy. Auriculotemporal nerve (Frey) syndrome. *Arch Dermatol* 1997;133(9):1143–5.
 88. Sethuraman G, Mancini AJ. Familial auriculotemporal nerve (Frey) syndrome. *Pediatr Dermatol* 2009;26(3):302–5.
 89. Listernick R, Legius E, Charrow J. Gustatory flushing (auriculotemporal nerve syndrome) in children with neurofibromatosis type 1 and facial plexiform neurofibromas. *J Pediatr* 2011;158(6):1034–1034.e1.
 90. Farman M, Zaitoun H. Auriculotemporal nerve syndrome in association with congenital haemangiopericytoma: a case report. *Eur J Paediatr Dent* 2010;11(4):213–15.
 91. Lance JW, Drummond PD, Gandevis SC, et al. Harlequin syndrome: the sudden onset of unilateral flushing and sweating. *J Neurol Neurosurg Psychiatry* 1988;51(5):635–42.
 92. Indo Y, Tsuruta M, Hayashida Y, et al. Mutations in the TRKA/NGF receptor gene in patients with congenital insensitivity to pain with anhidrosis. *Nat Genet* 1996;13(4):485–8.
 93. Zaenglein AL, Chang MW, Meehan SA, et al. Extensive Riga–Fede disease of the lip and tongue. *J Am Acad Dermatol* 2002;47(3):445–7.

Lumps, Bumps, and Hamartomas

JULIE S. PRENDIVILLE

Lumps and bumps

A wide variety of conditions affecting the skin and subcutaneous tissues present as papulonodular lesions, or 'lumps and bumps.' Benign and malignant neoplasms, hamartomas, and inflammatory and infectious disorders, as well as a number of infiltrative diseases, can be included in this category. Some of these conditions are discussed in detail in other chapters. This section deals with a group of nonmalignant disorders that present as discrete, circumscribed skin lesions or hamartomas in newborns and young infants.

FIBROMATOSES

The fibromatoses represent a diverse collection of mesenchymal tumors characterized by fibroblastic–myofibroblastic proliferation.¹ They are locally invasive neoplasms that do not metastasize but which may recur following surgical excision. They vary in clinical behavior, from benign lesions that regress spontaneously to aggressive life-threatening tumors. They can be solitary or multifocal, and may exhibit skin, soft tissue, bone, or visceral involvement. Most of these tumors are sporadic, but some occur in a familial setting.

The fibromatoses are classified as juvenile or adult (Box 26.1).¹ The juvenile fibromatoses are a unique group of fibroblastic–myofibroblastic proliferations that present at birth or in the first years of life (Table 26.1), accounting for approximately 12% of pediatric soft tissue tumors.¹ Adult-type fibromatoses are occasionally observed in infancy and childhood.¹ The fibromatoses have also been subdivided according to the site of fibrous tissue overgrowth into superficial or fascial, and deep or musculoaponeurotic (desmoid type).²

Infantile myofibromatosis

The term infantile myofibromatosis was introduced by Chung and Enzinger³ in 1981 to designate a disorder previously described under numerous synonyms, including congenital multiple fibromatosis, diffuse congenital fibromatosis, multiple congenital mesenchymal tumors, and multiple vascular leiomyomas of the newborn. There are three clinical patterns of presentation: solitary infantile myofibroma; multicentric infantile myofibromatosis, with multiple lesions in the skin, soft tissues, and bone; and generalized infantile myofibromatosis, in which there is also visceral involvement.¹

Cutaneous findings. Over 80% of myofibromas present in the first 2 years of life, and 60% are apparent at birth or shortly thereafter.^{3,4} Lesions may be superficial or deep, involving the skin, subcutaneous tissues, and muscle. They appear clinically as discrete, rubbery, firm to hard nodules measuring from 0.5

to 8 cm in diameter (Fig. 26.1). Cutaneous myofibromas may be skin-colored or have a prominent vascular appearance, resembling hemangioma. Sites of predilection for solitary lesions are the head, neck, trunk, and upper extremities. In the multicentric and generalized forms there are multiple and widespread myofibromas, numbering from a few to over 100 (Fig. 26.2).⁵ Skin and soft tissue lesions are asymptomatic and usually cause little morbidity. Rarely, a myofibroma presents with surface ulceration or an atrophic morphology (Fig. 26.3).^{4,6} Joint contractures have been observed with extensive limb lesions.⁷

Extracutaneous findings. In the multicentric form of the disease, myofibromas in the skin and soft tissues are associated with multiple lytic bone lesions. These may be extensive and can involve any bone.⁵ Progression in size and number has been observed during infancy.⁵ The bone tumors eventually stabilize, and spontaneous healing occurs with complete regression during the first few years of life. The development of sclerotic borders around lytic areas may be an early sign of regression.⁵ In most cases, there are no clinical signs or symptoms of bone disease. Pathologic fractures may occur rarely and usually heal without residual deformity.^{5,8} Vertebral body collapse has been described, with residual loss of vertebral height in early childhood.⁵ There are reports of spinal cord compression resulting from solitary or multicentric lesions involving the spinal canal.⁹ Solitary infantile myofibroma may also occur in the orbit.¹⁰

The much rarer generalized form of infantile myofibromatosis is characterized by involvement of visceral organs in addition to skin, soft tissue, and bone tumors. The gastrointestinal tract, heart, and lungs are most frequently affected. Involvement of the central nervous system is rare. Myofibromatosis in visceral organs is locally invasive and may severely compromise organ function. Cardiopulmonary, gastrointestinal, and hepatobiliary complications can be fatal, particularly in the newborn period or early infancy.¹¹ There have been two reports of associated aneurismal dilatations of arteries as observed in fibromuscular dysplasia.¹²

Multiple skin and soft tissue tumors may occasionally occur in the absence of bone or visceral involvement.¹ Conversely, bone involvement has been observed in association with a single soft tissue lesion,¹¹ or in the absence of skin lesions.⁵

Etiology and pathogenesis. The pathogenesis is unknown. Most cases are sporadic. Familial occurrence is associated with autosomal dominant inheritance.¹³

Diagnosis. Myofibromatosis may be suspected by the presence of firm, cutaneous and subcutaneous nodules. A biopsy is required to confirm the diagnosis. All three forms of infantile

myofibromatosis show interlacing fascicles of spindle-shaped fibroblasts.¹ Central vascular areas resembling hemangiopericytoma are variably present. Focal necrosis, calcification, hyalinization, macrophages containing hemosiderin, and chronic inflammation may be seen.¹ A giant cell variant containing multiple multinucleated giant cells has also been described. There is positive immunoreactivity for vimentin and actin,

consistent with the presumed myofibroblastic derivation of the tumor; desmin staining is variable. Electron microscopy shows cells with features of both fibroblasts and smooth muscle cells.

Infants with cutaneous myofibromas should be evaluated for bone and visceral involvement, particularly when there are multiple lesions. Recommended initial investigations include a skeletal survey, chest X-ray, echocardiogram, and abdominal imaging studies.¹¹

Differential diagnosis. Infantile myofibromatosis can be distinguished from other pediatric soft tissue tumors by

BOX 26.1 FIBROMATOSES OF THE SKIN AND SOFT TISSUES

JUVENILE FIBROMATOSES

- Infantile myofibromatosis
- Infantile desmoid-type fibromatosis^a
- Fibromatosis colli
- Infantile digital fibromatosis
- Fibrous hamartoma of infancy
- Lipofibromatosis^a
- Gingival fibromatosis
- Juvenile hyaline fibromatosis
- Infantile systemic fibromatosis

ADULT-TYPE FIBROMATOSES

Superficial

- Superficial palmar plantar fibromatosis^a
- Knuckle pads

Deep

- Desmoid fibromatosis^a

^aDenotes potentially locally aggressive tumors

(Adapted from Coffin CM, Alaggio R. Fibromyoblastic and myofibroblastic tumors in children and adolescents. *Pediatr Dev Pathol* 2012; 15(Suppl 1):127–180.)



Figure 26.1 Skin-colored nodule in infantile myofibromatosis.

TABLE 26.1

Juvenile fibromatoses

	Location	Inheritance	Associated features	Course	Treatment
Infantile myofibromatosis	Solitary, multicentric or generalized	Sporadic, autosomal dominant	Lytic bone lesions, visceral involvement	Spontaneous regression of bone and skin lesions; visceral lesions may be fatal	Await spontaneous regression, local excision if necessary; '?' chemotherapy or radiation for visceral lesions
Infantile desmoid-type fibromatosis	Any site	Usually sporadic, autosomal dominant	Other congenital anomalies	Locally invasive; does not metastasize; recurs after excision	Local excision with wide margins; '?' chemotherapy for non-resectable lesions
Fibromatosis colli	Neck	Rarely familial	None	Spontaneous regression	Physiotherapy
Infantile digital fibromatosis	Fingers and toes	Sporadic	None	Spontaneous regression reported; may recur	Await spontaneous regression; local excision if necessary
Fibrous hamartoma of infancy	Axillae, shoulders, chest wall	Sporadic	None	Does not regress	Local excision
Gingival fibromatosis	Gums	Autosomal dominant, recessive	Generalized hypertrichosis	May interfere with ability to eat, speak	Surgical debulking
Juvenile hyaline fibromatosis	Nodules on face and elsewhere	Autosomal recessive	Gingival hypertrophy, joint contractures	Chronic physical and cosmetic disability, overlaps with ISH	Supportive care, surgical excision of nodules if necessary
Infantile systemic hyalinoses (ISH)	Generalized thickening of skin	Autosomal recessive	Painful joint contractures, protein-losing enteropathy	Usually fatal within first few years of life	Supportive care



Figure 26.2 Multicentric cutaneous myofibromas in an infant with extensive bone lesions. This case was familial, with autosomal dominant transmission.



Figure 26.3 Infantile myofibroma presenting as a congenital area of atrophy and telangiectasia with central red nodules, one of which was ulcerated.

histopathologic examination of biopsy material. These include other forms of fibromatosis, as well as congenital fibrosarcoma, leiomyoma and leiomyosarcoma, neurofibroma, metastatic neuroblastoma, hemangioma, hemangiopericytoma, chondromatosis, stiff skin syndrome, and nodular fasciitis.¹

Treatment and prognosis. The prognosis for infantile myofibromatosis is good in the absence of visceral involvement. Lesions in the skin and soft tissues show spontaneous involution during the first few years of life, sometimes leaving residual areas of skin atrophy or hyperpigmentation (Fig. 26.4). Bone lesions also regress spontaneously, usually without significant disability or residual radiologic change. They do not interfere with enchondral bone growth.⁵ The prognosis is grave for newborns with visceral disease, in whom a mortality rate of 76% has been documented.¹¹

Surgical excision may be necessary to obtain tissue for diagnosis. Otherwise, excision should be limited to lesions that result in functional impairment or severe cosmetic disability.^{7,11} The role of chemotherapy or radiation for symptomatic, recurrent, or nonresectable disease is not established. Successful

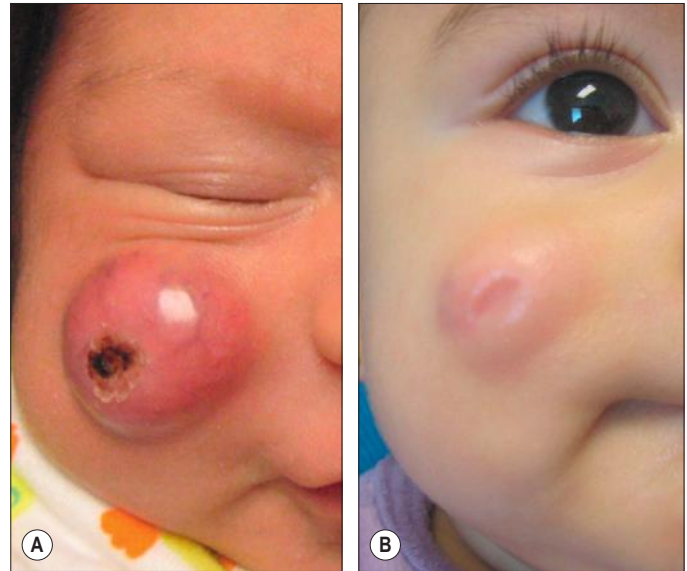


Figure 26.4 Infantile myofibroma with (A) central ulceration at 5 weeks of age and (B) spontaneous involution with scarring at 5 months. (Courtesy of Linda Beets-Shay, MD.)

treatment of life-threatening generalized infantile myofibromatosis and multicentric disease using low-dose chemotherapy has been reported.¹⁴

Infantile desmoid-type or aggressive fibromatosis

Although desmoid fibromatosis has traditionally been considered a deep fibromatosis of adulthood, with abdominal, intra-abdominal, and extra-abdominal variants, a specific juvenile subset is recognized.¹ Description of this entity under a variety of synonyms, including among others aggressive fibromatosis of infancy, musculoaponeurotic fibromatosis, desmoma, and fibrosarcoma grade 1 desmoid type, has led to confusion in the literature.¹⁵ Up to 30% of juvenile desmoid tumors present in the first year of life, and congenital cases have been reported.^{1,16}

Clinical findings. Infantile desmoid-like or aggressive fibromatosis involves deep tissues and is generally extra-abdominal.¹ The usual clinical presentation is a slowly growing, nontender subcutaneous mass that has been present for weeks or months (Fig. 26.5). Sites of predilection in children are the head and neck, extremities, shoulder girdle, trunk, and hip regions. The abdomen, retroperitoneum, spermatic cord, and breast may also be involved. Rarely, there are multiple lesions. The tumor tends to be very locally aggressive, with infiltration of adjacent skeletal muscles, tendons, or periosteum, and erosion of bone.

Approximately 12% of pediatric patients with desmoid fibromatosis have other congenital abnormalities.¹ Adult-type intra-abdominal desmoid tumors are associated with familial adenomatous polyposis (FAP) and Gardner syndrome.^{1,17} Although most tumors in children are sporadic, there are reported cases of associated Gardner syndrome in childhood, one of which presented in infancy.^{18–20}

Etiology and pathogenesis. The finding of minor radiologic bone abnormalities in 80% of patients with desmoids and 48% of their relatives suggests an autosomal dominant mode of inheritance.¹ Antecedent trauma, including surgery or



Figure 26.5 Desmoid fibromatosis: firm mass on the thigh of an infant, diagnosed as 'aggressive fibromatosis of infancy.'

irradiation, is reported in 12–63% of patients with all forms of desmoid tumor.¹ It is postulated that desmoid tumors are associated with a familial defect in the regulation of connective tissue and may be precipitated by multiple factors.^{1,17,21} Desmoid fibromas in adults and children can be associated with mutations in the adenomatosis polyposis coli (*APC*) or β -catenin *CTNNB1* genes.²²

Diagnosis. The tumor is composed of bundles of slender, uniform spindle cells surrounded by variable amounts of collagen. Cleft or slit-like blood vessels are variable in number and more abundant at the periphery. The fibrous proliferation may be indistinguishable from scar tissue, except that it infiltrates skeletal muscle and tendons. Cellularity is variable. Some childhood lesions have an increased number of mitoses and greater cellularity.¹ Immunohistochemical and ultrastructural studies show that the lesion is composed of fibroblasts and myofibroblasts. Immunohistochemistry and genotyping may help to distinguish sporadic from FAP cases.²²

Differential diagnosis. Myofibromatosis and other juvenile fibromatoses should be considered in the differential diagnosis. Keloid scars are more superficial than desmoid tumors. Cellular variants must be distinguished histopathologically from fibrosarcoma.

Treatment and prognosis. Local excision with wide margins, if possible, is the mainstay of treatment.^{16–19,23} The recurrence rate varies from 30–80%.¹ Higher recurrence rates are associated with a young age at diagnosis, large lesions, intralesional or marginal excision, and intra-abdominal location. Microscopic features of high vascularity, myxoid foci, and abundant immature myofibroblasts are associated with a higher recurrence rate.¹ Treatment with combination chemotherapy and radiotherapy, or with tamoxifen and nonsteroidal anti-inflammatory agents, has been advocated for nonresectable, symptomatic or progressive disease.^{19,24} Mortality from locally aggressive desmoids is less than 10%.¹

Fibromatosis colli

Fibromatosis colli, also known as sternocleidomastoid pseudo-tumor of infancy or congenital muscular torticollis, is a congenital fibromatosis of the sternocleidomastoid muscle. It occurs in up to 0.4% of live newborns.¹ Males are affected more than females. It does not involve the skin.

Clinical findings. A hard, nontender, lobulated subcutaneous mass is palpable in the lower third of the sternocleidomastoid muscle. The trapezoid muscle is sometimes involved. Following an initial rapid period of growth, the tumor stabilizes in size. Torticollis and facial asymmetry are variable and may be transient. There is a right-sided predominance, and 2–3% of cases are bilateral.¹

Etiology and pathogenesis. The pathogenesis is unknown. Birth trauma has been implicated in 50% of cases, with a history of complicated delivery; whether this is a cause or an effect of the tumor is not clear. Familial cases are rare.¹

Diagnosis. Histopathologically, bands of fibroblasts with abundant collagen are intermingled with residual angulated skeletal muscle fibers. The diagnosis may be established by fine-needle aspiration, which shows benign spindle cells and degenerating skeletal muscle fibers. Ultrasound or magnetic resonance imaging may also be useful.²⁵

Differential diagnosis. A combination of the typical location of the lesion in the neck and the characteristic histopathology is diagnostic. The clinical differential diagnosis of a neck swelling includes lymphatic malformation, hemangioma, and malignant neoplasms. The histopathologic features may resemble those of a desmoid tumor.¹

Treatment and prognosis. The majority of lesions regress within the first year of life. Most resolve completely, but minor residual asymmetry or tightening of the sternocleidomastoid muscle is seen in 25% of cases.¹ Only 9% have persistence of the tumor and torticollis. Physiotherapy is the treatment of choice.²⁶ Surgery is rarely necessary unless the diagnosis is in doubt or the mass fails to resolve.

Infantile digital fibromatosis

Infantile digital fibromatosis is a recurring myofibroblastic proliferation of the fingers and toes. Synonyms for this tumor include digital fibrous tumor of Reye, digital fibrous swelling, recurring digital fibrous tumor of childhood, and inclusion body fibromatosis.¹

Cutaneous findings. Almost all lesions are diagnosed in infancy, and one-third are present at birth. Both sexes are affected equally. The typical lesion is an asymptomatic, firm, smooth, pink nodule located on the lateral or dorsal aspect of the digit, measuring <3 cm in diameter (Fig. 26.6). Lesions are more common on the fingers than on the toes. The thumbs and great toes are spared. There is often deformity of the affected digit. There may be single or multiple nodules (Fig. 26.7). Rarely, more than one digit is involved or extradigital lesions are seen.²⁷

Extracutaneous findings. Periosteal attachment is not unusual, but underlying bone erosion is rare.



Figure 26.6 Infantile digital fibroma presenting as a smooth, pink nodule.



Figure 26.7 Infantile digital fibroma.

Etiology and pathogenesis. The pathogenesis is not known. Defective organization of actin filaments in myofibroblasts has been hypothesized.¹

Diagnosis. Whorls and interdigitating sheets of uniform fibroblasts in a densely collagenous stroma are seen in the dermis or subcutis.¹ A unique feature is the presence of distinctive, eosinophilic, perinuclear cytoplasmic inclusions surrounded by a clear halo that stain red with a trichrome stain. Electron microscopy shows abundant cytoplasmic filaments that form whorled bodies; these are the ultrastructural correlate of the cytoplasmic inclusions. Immunostaining is positive for desmin, actin, vimentin, and keratin.

Differential diagnosis. The digital location and the characteristic histopathology distinguish this lesion from other fibromatoses and pediatric soft tissue tumors.

Treatment and prognosis. The local recurrence rate is 60–90% following surgical excision. Many tumors regress spontaneously within a few years.²⁷ Conservative management without surgery is appropriate, unless there is functional impairment.²⁷ Mohs micrographic surgery to debulk the tumor has been performed.²⁸ Successful treatment with intralesional fluorouracil injections has been reported in a 7-year-old child.²⁹

Fibrous hamartoma of infancy

Fibrous hamartoma of infancy is a benign fibrous tumor that develops during the first 2 years of life.³⁰ Up to 20% are present at birth.¹ Occasional cases have been described in children between 2 and 10 years. Males are affected more frequently than females.

Cutaneous findings. Fibrous hamartoma presents as a subcutaneous lesion located around the axillae, shoulders, and upper chest wall.³¹ It may involve other sites, such as the inguinal region, extremities, and head and neck. It is usually a solitary nodule, measuring 2–5 cm in diameter, that feels lumpy to palpation. There may be overlying hypertrichosis. Occasionally, these lesions are multifocal. There are no symptoms.

Extracutaneous findings. There are no systemic associations.

Etiology and pathogenesis. Fibrous hamartoma of infancy is believed to represent a hamartomatous process rather than a true neoplasm. It is not familial.

Diagnosis. The hamartoma is located in the subcutaneous and musculoaponeurotic tissues.^{30,31} Histopathologic examination reveals three characteristic elements: a fibrous component consisting of well-defined fascicles of fibroblasts or disorderly fibroblasts in a collagenous stroma; mature adipose tissue; and myxoid mesenchymal tissue in a basophilic matrix. Electron microscopy reveals the presence of both fibroblasts and myofibroblasts, primitive mesenchymal cells, small blood vessels, and mature adipocytes.¹

Differential diagnosis. The clinical differential diagnosis of fibrous hamartoma of infancy includes a macrocystic lymphatic malformation, hemangioma, and other soft tissue tumors. Identification of the three histopathologic components of this lesion distinguishes it from other fibroblastic proliferations.³¹ A similar hamartoma with an admixture of fat and an absence of fibromyxoid tissue is described as lipofibromatosis.³²

Treatment and prognosis. There is no tendency to spontaneous regression. The treatment of choice is surgical excision. The recurrence rate is low, even with incomplete excision.³¹

Lipofibromatosis

Lipofibromatosis is a rare, slowly growing tumor of fibroblasts and mature adipose tissue.¹ It affects infants and young children and is congenital in up to 25% of cases. The tumor typically arises on the distal extremities and is less often encountered on the head and neck.¹ Lesions range in size from 2–7 cm in diameter.

Histopathologically, there is abundant adipose tissue traversed by fascicles of fibroblasts with variable collagen and focal myxoid change. Spindle cells stain positive for smooth muscle actin.

The differential diagnosis of lipofibromatosis includes fibrolipoma, lipofibromatous hamartoma, fibrous hamartoma of infancy, lipoblastoma, and desmoid fibromatosis. Treatment is by surgical resection but the rate of recurrence or persistent growth is high.

Gingival fibromatosis

This is a rare familial disorder that manifests at the time of eruption of the deciduous or permanent teeth.

Cutaneous findings. There is slowly progressive gingival enlargement that may cover the crowns of the teeth and result in difficulty in eating or speaking. It is associated with generalized hypertrichosis.

Extracutaneous findings. Rarely there is associated mental retardation and epilepsy. The Zimmerman–Laband syndrome is characterized by gingival fibromatosis, hypertrichosis, intellectual disability, and absence and/or hypoplasia of the nails or terminal phalanges of the hands and feet as well as other anomalies.³³

Etiology and pathogenesis. Inheritance is most commonly autosomal dominant and the disorder has been mapped to loci on chromosomes 2 and 5.^{34,35} Autosomal recessive and sporadic cases are also reported.³⁶

Diagnosis. Mucosal biopsy shows coarse, interlacing collagen bundles with sparse fibroblasts and myofibroblasts. There may be calcification, ossification, abundant amorphous extracellular material, and cellular fibroblastic proliferation.

Differential diagnosis. The differential diagnosis includes phenytoin usage, chronic gingivitis, cherubism, juvenile hyaline fibromatosis, and other rare syndromes.

Treatment and prognosis. Treatment options include repeated surgical debulking of the gums or dental extraction.

ADULT-TYPE FIBROMATOSES

The superficial fibromatoses of adulthood are the most common type of fibromatosis in the general population but are rare in infants and children. Fibromatosis may involve the palm (Dupuytren contracture), the plantar surface of the foot (Ledderhose disease), or the penis (Peyronie disease). Dupuytren-type fibromatosis of the palms and soles may be seen in childhood, and is occasionally congenital (Fig. 26.8).¹ Surgical excision is only necessary for diagnosis or for release of contractures. Knuckle pads are seen in older children and adolescents but not in infants.

Leiomyoma

Leiomyoma is a benign tumor of smooth muscle. Cutaneous leiomyoma may arise from the arrector pili muscle in hair follicles, the dartos muscle of the scrotum and labia majora, the erectile muscle of the nipple, and the muscular wall of veins (angioleiomyoma). Leiomyomas are uncommon in children and are extremely rare in the newborn period.³⁷

Cutaneous findings. Cutaneous leiomyomas appear as discrete papules or nodules with a pink or brown discoloration of the overlying skin. They are usually solitary but may be multiple. Rarely, a leiomyoma may present as a pedunculated mass at birth or as a papular plaque in early infancy.^{37–39} Leiomyomas are often painful, particularly on exposure to cold. Leiomyomas of the tongue are also reported.³⁸

Extracutaneous findings. Most cutaneous leiomyomas are not associated with visceral disease. The multiple leiomyomas of the esophagus and tracheobronchial tree in Alport syndrome may be associated with female genital leiomyomas in older children and adults.⁴⁰ Leiomyomas that occur in immunocompromised children only rarely involve the skin or soft tissues.⁴¹

Etiology and pathogenesis. Multiple cutaneous leiomyomas presenting in adolescence or adult life may be inherited as an autosomal dominant trait, but the etiology of other forms is unknown.

Diagnosis. The diagnosis is made by skin biopsy, which demonstrates whorls and bundles of well-differentiated spindle cells with cigar-shaped nuclei in the dermis. There is a variable collagenous component. The smooth muscle stains red with the Masson trichrome stain. Immunohistochemistry is positive for muscle-specific actin and desmin reactivity.

Differential diagnosis. Leiomyoma must be distinguished from the fibroblastic and myofibroblastic proliferations of infancy and childhood, as well as from other spindle cell tumors such as neurofibroma and leiomyosarcoma. Immunohistochemistry may be helpful, as myofibroblastic tumors express smooth muscle actin more than muscle-specific actin or desmin.³⁷ The circumscribed spindle cell appearance of leiomyoma differs from the smooth muscle bundles of congenital smooth muscle hamartoma.

Treatment and prognosis. Excision is curative for solitary lesions.

NEUROFIBROMAS AND OTHER NEURAL TUMORS

Cutaneous neurofibromas in infants and young children are most frequently associated with neurofibromatosis type 1 (NF-1) (see Chapter 29). These benign tumors consist of Schwann cells, nerve fibers, and fibroblasts, and may be cutaneous, subcutaneous, or plexiform. Cutaneous and subcutaneous neurofibromas are rarely seen at birth but may sometimes appear within the first year of life. Plexiform neurofibromas are often present at birth and are considered pathognomonic of neurofibromatosis. There may be a large area of hyperpigmentation overlying the plexiform neurofibroma that predates the characteristic ‘bag of worms’ consistency of the tumor. These lesions enlarge with time and can cause considerable cosmetic disfigurement, particularly on the face and around the eye. A plexiform neurofibroma in the neck may compromise airway function, and large lesions over the back are often associated with underlying spinal involvement.

Schwannomas are found in both neurofibromatosis type 2 (NF-2) and in schwannomatosis. Schwannomatosis, or neurilemmomatosis, is characterized by multiple cutaneous schwannomas and can present at birth or develop during childhood.⁴² These lesions are a marker for development of central nervous system tumors in later childhood and adult life. Schwannomatosis is sometimes associated with *SMARCB1* mutations and is distinguished from NF-2 primarily by the absence of vestibular tumors.⁴²



Figure 26.8 Congenital fibromatosis of the palm.

Pacinian neurofibromas, or nerve-sheath myxomas, are uncommon tumors with components that resemble Vater-Pacini corpuscles.⁴³ Multiple hairy pacinian neurofibromas have been reported in children without NF-1 and may be congenital.⁴³ Underlying skeletal anomalies may be associated with pacinian neurofibromas in a sacrococcygeal location.

NON-LANGERHANS' CELL HISTIOCYTOSES

The non-Langerhans' cell histiocytoses encompass a diverse group of disorders in which there is proliferation of mononuclear phagocytes other than Langerhans' cells. Two variants, juvenile xanthogranuloma and benign cephalic histiocytosis, occur primarily in infants and young children. Other benign histiocytoses, such as papular xanthoma, xanthoma disseminatum, and generalized eruptive xanthoma, may rarely present in childhood, but are extremely unusual in infancy.^{44,45}

Juvenile xanthogranuloma

Juvenile xanthogranuloma is a benign, self-healing, non-Langerhans' cell histiocytosis characterized by solitary or multiple yellow-red papules and nodules in the skin and occasionally in other organs.⁴⁶ Although adults may be affected, it is predominantly a disorder of infancy and early childhood. There is an increased frequency of juvenile xanthogranuloma in children with NF-1, juvenile myeloid leukemia, and urticaria pigmentosa.^{47,48} Juvenile xanthogranulomas have also developed in children with Langerhans' cell histiocytosis either concurrently or at a later date.⁴⁹ There are single case reports of coexistence with Wiskott-Aldrich syndrome and acute lymphoblastic leukemia.^{50,51}

Cutaneous findings. The typical juvenile xanthogranuloma is an asymptomatic, firm, well-demarcated papule or nodule that measures from 1 mm to 2 cm in diameter. Early lesions are pink or red in color, later changing to a distinctive yellow or orange-brown (Fig. 26.9). There may be overlying telangiectasia with a purpuric appearance, and occasionally surface ulceration and bleeding with associated pruritus and discomfort. Solitary lesions with a hyperkeratotic surface, pedunculated or plaque-like morphology are also reported.⁴⁶ As many as 17% of juvenile xanthogranulomas are present at birth, and 70% develop within the first year of life.⁴⁶ The majority are solitary lesions. Multiple



Figure 26.9 Juvenile xanthogranuloma.

lesions may be few or number in the hundreds (Fig. 26.10A). They can be located at virtually any body site, but are most common on the head, neck, and upper trunk.

Juvenile xanthogranulomas may be classified as micronodular, measuring 2–5 mm, or macronodular, measuring 0.5–2 cm in diameter. An unusual variant is the giant juvenile xanthogranuloma, which measures from 2–10 cm in diameter (Fig. 26.10B).⁵² These lesions are congenital or appear in early infancy and may have a greater propensity to ulcerate. Rarely, numerous micronodular lesions may present as a generalized lichenoid eruption.⁵³

Extracutaneous findings. Extracutaneous juvenile xanthogranuloma is rare, and less than 50% of these patients have associated cutaneous lesions.⁵⁴ The most frequent extracutaneous sites are the eye and orbit, central nervous system, liver/spleen, lung, oropharynx, and muscle. In contrast to cutaneous lesions, a systemic juvenile xanthogranuloma may produce symptoms related to a mass effect or infiltration of the involved organ. The incidence of ocular disease in patients with cutaneous lesions is 0.3–0.4%.⁵⁵ Eye lesions manifest as an asymptomatic mass on the iris, unilateral glaucoma, spontaneous hyphema, or color change of the iris. Risk factors for eye involvement include multiple lesions, age <2 years, and recently diagnosed disease.⁵⁵

Juvenile xanthogranulomas are seen with increased frequency in patients with NF-1. A triple association between



Figure 26.10 (A) Multifocal juvenile xanthogranulomas in an infant. (B) Giant juvenile xanthogranuloma with ulceration.

juvenile chronic myeloid leukemia, juvenile xanthogranulomas, and NF-1 is recognized (Fig. 26.11).⁴⁷

Etiology. The etiology of juvenile xanthogranuloma is unknown. The precursor cell of the histiocytic proliferation is believed to be the interstitial/dermal dendrocyte.⁵⁶ The observed occurrence in monozygotic twins may suggest a genetic predisposition.^{57,58}

Diagnosis. The typical histopathologic appearance consists of a dense dermal infiltrate of foamy histiocytes with Touton giant cells. There is an admixture of other cell types, including lymphocytes, eosinophils, neutrophils, and foreign body giant cells, as well as infrequent mitoses. In early lesions, there may be few or absent foam cells or Touton giant cells, with a variable number of spindle cells and numerous mitotic figures.⁵⁹ Immunohistochemistry shows negative staining for S100 and CD1a, and positive staining for factor X111a, CD68, CD163, fascin and CD14.⁵⁶ There are no Birbeck granules visible on ultrastructural examination.

Differential diagnosis. Distinguishing a small juvenile xanthogranuloma from clinically similar lesions such as xanthoma, mastocytoma, Spitz nevus, and other benign skin tumors may require a skin biopsy. Giant lesions may be mistaken for a hemangioma or malignant tumor. Early lesions that lack the characteristic lipid-laden histiocytes and Touton giant cells may resemble Langerhans' cell histiocytosis on histopathologic examination.^{56,59} The absence of Birbeck granules and negative staining for S100 is characteristic of juvenile xanthogranuloma.

Treatment and prognosis. Most cutaneous lesions resolve spontaneously over months or years and do not require treatment. Ulcerating, symptomatic, or large unsightly lesions may require surgical excision. A residual area of hyperpigmentation or anetoderma-like atrophy may persist. Ocular and systemic lesions can be more problematic and involvement of the liver and bone marrow can be life-threatening.⁶⁰ Treatment options include observation, corticosteroids, surgical excision, radiation therapy, and chemotherapy.^{46,60}

Benign cephalic histiocytosis

Benign cephalic histiocytosis is a non-Langerhans' cell histiocytosis characterized clinically by multiple brownish-yellow macules and papules on the face and adjacent areas. Some authors believe that benign cephalic histiocytosis is a variant of micronodular juvenile xanthogranuloma.^{61,62}

Cutaneous findings. Lesions first appear between the ages of 2 months and 2 years. The face is the site of predilection, but the scalp, neck, and ears can also be involved. Lesions may be scattered over the shoulders and upper arms. Typical lesions are slightly raised, asymptomatic papules measuring 2–3 mm in diameter that vary from erythematous to light-brown or yellowish in color (Fig. 26.12). The mucous membranes are not involved.

Extracutaneous findings. Typically, extracutaneous disease is absent, but there has been one report of associated diabetes insipidus.⁶³

Diagnosis. Histopathologically, a monomorphous histiocytic infiltrate is located in the upper and mid-dermis. There may

also be a few lymphocytes and eosinophils. Foamy macrophages and Touton giant cells are typically absent. Staining for S100 protein is usually negative.⁶⁴ Electron microscopy reveals coated vesicles and comma- or worm-shaped bodies. Birbeck granules are absent.

Differential diagnosis. The differential diagnosis includes juvenile xanthogranuloma, Langerhans' cell histiocytosis, and cutaneous mastocytosis. The lesions of mastocytosis have a similar color but urticate when rubbed (Darier sign) and have a distinctive histology. Benign cephalic histiocytosis can be distinguished from Langerhans' cell histiocytosis by immunohistochemical stains and the absence of Birbeck granules on electron microscopy.

Treatment and prognosis. There is no effective treatment. The skin lesions regress spontaneously over months to years. There may be residual hyperpigmentation and anetoderma-like atrophy.

Calcifying disorders of the skin

Calcium deposition in the skin, or calcinosis cutis, is found in a diverse group of disorders. It is termed dystrophic calcification when calcium is deposited in abnormal or injured tissue in patients with no abnormality of calcium or phosphate metabolism. Metastatic calcification develops in normal tissues as a result of abnormal calcium and phosphorus metabolism. Idiopathic calcification occurs in the absence of any discernible tissue injury or metabolic abnormality. Iatrogenic calcification may develop as a complication of calcium infusions or the application of calcium-containing paste to abraded skin. Cutaneous ossification, in which normal bone is formed in the dermis and subcutaneous soft tissues, is termed osteoma cutis.

DYSTROPHIC CALCIFICATION

Dystrophic calcification arises at sites of skin trauma or in association with inflammatory lesions, connective tissue disorders, skin tumors, and cysts. Calcinosis cutis on the heels is a not uncommon sequela of drawing blood by heel sticks during the neonatal period.^{65,66} It presents some months later as one or more white papules or nodules, and usually resolves spontaneously by 18–30 months of age. Calcification may also occur in association with subcutaneous fat necrosis of the newborn.^{67,68} Calcium deposition has been observed histopathologically both in the septa and within the fat lobules.^{67,69} Widespread subcutaneous calcification may develop in cases of subcutaneous fat necrosis complicating hypothermic cardiac surgery.^{68–70} Although hypercalcemia is a known complication of subcutaneous fat necrosis, the majority of reported cases of soft-tissue calcification have occurred in normocalcemic patients. Conversely, most infants with subcutaneous fat necrosis and hypercalcemia do not show evidence of calcium deposition in biopsies taken from affected sites.⁶⁸

Dystrophic calcification has been reported in the skin lesions of a newborn infant with intrauterine-acquired herpes simplex infection.⁷¹ The calcification was present at birth and appeared to have developed in utero. A lethal disorder characterized by extensive congenital skin necrosis and follicular calcification has been described in three newborn females.⁷² Dystrophic



Figure 26.11 (A) Multiple juvenile xanthogranulomas and (B) café-au-lait macules in a child with juvenile chronic myeloid leukemia.



Figure 26.12 Infant with benign cephalic histiocytosis.

calcification may also occur as a complication of intralesional corticosteroid injection of infantile periocular hemangiomas.⁷³

METASTATIC CALCIFICATION

Metastatic calcification occurs when calcium salts are precipitated in normal tissues as a result of high serum calcium or phosphate levels. The calcium deposits usually consist of hydroxyapatite crystals. This is associated primarily with chronic renal insufficiency, in which ulceration of the skin may be caused by calcification of blood vessels, leading to ischemic skin necrosis, or by painful disseminated calcification of the dermis and subcutaneous tissues (calciophylaxis).⁷⁴ Chronic renal failure is also associated with benign nodular calcification. Cutaneous calcium deposits may develop as a result of hypervitaminosis D, milk-alkali syndrome, and other causes of hypercalcemia and hyperphosphatemia.

Metastatic calcinosis in the skin is rarely seen in infancy and childhood.⁷⁵ In contrast, the cutaneous bone formation, or osteoma cutis, associated with Albright hereditary osteodystrophy frequently appears first in infancy or childhood and may present in the neonatal period. This metabolic disorder is discussed below.

IDIOPATHIC CALCIFICATION

Idiopathic calcification can be congenital or acquired. Congenital calcified nodules occur most frequently on the ear, but may be seen elsewhere on the face and limbs. These lesions are variously described as congenital calcified nodule of the ear, subepidermal calcified nodule, or solitary congenital nodular calcification of Winer.^{76–78} Other types of idiopathic calcinosis cutis, such as idiopathic calcification of the scrotum or vulva, and the milia-like lesions associated with Down syndrome, present later in childhood or adolescence and are not seen in the newborn. There are rare reports of juxta-articular tumoral calcinosis in infancy.^{79–82}

Calcified ear nodule

A solitary calcified nodule on the pinna or earlobe is the most common presentation of idiopathic calcinosis in the newborn (Fig. 26.13). These nodules may occur elsewhere on the face or limbs, and occasionally there is more than one. Auricular lesions



Figure 26.13 Calcified ear nodule, also known as nodular calcification of Winer.

developing after birth have also been described. There is a male preponderance.

Cutaneous findings. The nodule is firm and measures 3–10 mm in diameter. The surface may be warty in appearance, or smooth and dome-shaped. The color is chalky white or yellow. Surface ulceration and discharge of calcified material may occur spontaneously or as a result of trauma. There are usually no associated symptoms.

Extracutaneous findings. Serum calcium and phosphate levels are normal. There are no systemic abnormalities.

Etiology and pathogenesis. The pathogenesis of these lesions is not clear. Most authors believe they represent dystrophic calcification following dermal damage from some unknown source. Proposed hypotheses include derivation from milia, syringomas, other sweat gland hamartomas, nevi, trauma, and ischemic injury.^{77,78}

Diagnosis. The diagnosis is often made on the clinical appearance. Histopathologically, amorphous and/or globular masses of calcified material are seen in the papillary dermis and may extend to the reticular dermis. Foreign body giant cells may be observed in association with the calcified masses. The overlying epidermis shows a warty architecture with variable amounts of pseudoepitheliomatous hyperplasia. Ulceration and transepidermal elimination of calcium may occur.

Differential diagnosis. Clinically, calcified nodules may be misdiagnosed as viral warts, molluscum contagiosum, pilomatricomas, syringomas, and congenital inclusion cysts.

Treatment and prognosis. If treatment is necessary, the nodule can be removed by curettage or excision. Calcified nodules sometimes recur following curettage or shave excision. Intralesional injection of triamcinolone at the time of shave excision has been suggested for recurrent lesions.⁷⁶

Tumoral calcinosis

Tumoral calcinosis is characterized by painless, calcified soft tissue nodules located close to large joints in otherwise healthy children and adults.^{79–82} It may affect several family members and occurs most frequently in patients of African or Middle-Eastern descent. There have been reports of tumoral calcinosis presenting in infancy, and two in the neonatal period.^{81,83,84}

Cutaneous findings. Tumoral calcinosis presents as progressively growing, lobulated masses in a juxta-articular location. The hip joints, shoulders, and elbows are most frequently affected in older children and adults. A predilection for the anterior aspect of the knee has been noted in three infants.⁸¹ Involvement of the buttock, axilla, and supraclavicular region has also been observed in infancy.⁸² Lesions may be multifocal and occasionally bilateral. Rarely, ulceration of the overlying skin with discharge of a chalky-white substance may occur.⁸⁰ Large lesions may interfere with joint or muscle function.

Extracutaneous findings. One subtype of tumoral calcinosis is associated with idiopathic hyperphosphatemia. Transient and marginally elevated serum phosphate levels were found in an affected infant.⁸¹ Serum calcium levels are normal.

Etiology and pathogenesis. Familial tumoral calcinosis with hyperphosphatemia has been linked to mutations in the *GALNT3* gene on chromosome 2q24, to the *KL* gene, encoding Klotho, and to the fibroblast growth factor-23 (*FGF-23*) gene.⁸⁴ Normophosphatemic familial tumoral calcinosis is linked to *SAMD9* mutations. Both subtypes have an autosomal recessive mode of inheritance.⁸⁴

Diagnosis. Radiographs show discrete, sometimes lobulated, calcified areas. There is no joint involvement, and the underlying bones appear normal. Excisional biopsy specimens usually show a well-encapsulated calcified mass, but there may be invasion of the surrounding musculature. Histopathologic examination reveals calcification, central necrosis, a chronic inflammatory cell infiltrate including multinucleate giant cells, and fibrosis.^{79,81}

Treatment. Excision is the treatment of choice, but there may be recurrence after excision. Spontaneous resolution was observed in one infant after incisional biopsy of a supraclavicular mass.⁸²

IATROGENIC CALCIFICATION

Iatrogenic calcinosis cutis (see [Chapter 8](#)) may result from intravenous infusion of calcium gluconate, with or without extravasation of the solution into the tissues. In addition to cutaneous calcification there may be an intense inflammatory response and occasionally soft tissue necrosis.⁸⁵

Iatrogenic calcification has also been described following electrode placement for electroencephalography, electromyography, and brainstem auditory evoked potentials when calcium-containing electrode paste was applied to abraded skin.⁸⁶ Treatment is generally symptomatic, and resolution occurs spontaneously over several months.

OSTEOMA CUTIS

Osteoma cutis is caused by heterotopic differentiation of osteoblasts in the dermis. It is classified as primary and secondary. In primary osteoma cutis there is no pre-existing skin pathology. In secondary osteoma cutis bone formation develops within scars, inflammatory lesions, skin tumors, hamartomas, or cysts.

Primary osteoma cutis may present in infancy as a manifestation of pseudohypoparathyroidism type 1 (PHP1), pseudopseudohypoparathyroidism (PPHP), or progressive osseous heteroplasia (POH).^{87,88} Congenital plate-like osteoma cutis (POC)⁸⁹ and reported cases of familial ectopic ossification or hereditary osteoma cutis may be related variants.⁹⁰

Pseudohypoparathyroidism type 1 and Albright hereditary osteodystrophy

Pseudohypoparathyroidism type 1 (PHP1) is characterized by a lack of end-organ responsiveness to parathormone and variable degrees of hypocalcemia and hyperphosphatemia. PHP1 can be associated with the phenotype of Albright hereditary osteodystrophy (AHO), a related clinical syndrome associated with PHP1 or PPHP. PPHP patients have the phenotype of AHO but serum calcium and phosphate levels are normal. Both PHP1 and PPHP may occur in the same kindred, although not in the same sibship.⁸⁷



Figure 26.14 Osteoma cutis presenting as hard dermal nodules with overlying skin discoloration.

Cutaneous findings. Osteoma cutis is present in up to 42% of patients with PHP1 and PPHP. Lesions are usually first noted in infancy or childhood. They may be located anywhere on the body and have a predilection for sites of friction or mild trauma. The characteristic lesions are blue-tinged, stone-hard papules, nodules, or plaques that range in size from pinpoint to 5 cm in diameter ([Fig. 26.14](#)). Early lesions may present as blue or erythematous macules ([Fig. 26.15](#)). Rarely, more extensive or deeper cutaneous ossification or POH may develop ([Fig. 26.16](#)). Ulceration occurs occasionally.

Extracutaneous findings. The characteristic phenotype of AHO includes short stature, round face, obesity, and brachydactyly, in particular a shortened fourth metacarpal. Other manifestations include dental defects, short broad nails, cataracts, calcification of the basal ganglia, and variable degrees of mental retardation. These findings are easier to discern in late childhood and adulthood than in infancy. Hypocalcemia may result in seizures and tetany. Most patients with PHP1 have thyroid stimulating hormone (TSH) resistance and hypothyroidism may occasionally present in the neonatal period. Hypogonadism and growth hormone resistance may also occur.

Etiology and pathogenesis. The metabolic changes in PHP result from a failure of receptors in renal and skeletal target tissues to respond to PTH. This resistance to the action of PTH is variable in PHP and absent in PPHP. End-organ resistance to PTH in PHP1 is associated with reduced expression or function of a guanine nucleotide stimulatory protein (Gs- α) that is required for activation of adenylate cyclase by the hormone-bound receptor.⁸⁷ This protein is encoded by the *GNAS1* gene located on chromosome 20q13. Inheritance is by autosomal dominant transmission. AHO with hormone resistance (PHP1) occurs only with maternal transmission of the genetic defect, whereas paternal imprinting results in PPHP or POH.⁹¹ The reason for development of cutaneous ossification is unclear but may relate to differentiation of dermal mesenchymal cells into osteoblasts.⁹²

Diagnosis. Skin histopathology shows bone formation in the dermis and subcutis. Osteoblasts, osteocytes, and osteoclasts are



Figure 26.15 Violaceous macules and papules of osteoma cutis in an infant with Albright hereditary osteodystrophy.



Figure 26.16 Progressive osseous heteroplasia in an infant with familial Albright hereditary osteodystrophy at 1 year of age.

present within the spicules of bone. When ossification is severe and progressive, a proliferation of spindle cells, resembling fibroblasts, may be prominent.

In PHP there is hypocalcemia, hyperphosphatemia, and an elevated serum PTH. In PPHP there is no discernible abnormality of calcium and phosphate metabolism. Urinary excretion of cAMP in response to intravenous infusion of PTH is impaired in most cases of PHP1, but is normal in PPHP.

Radiologic abnormalities include ossification of the skin and subcutaneous tissues; shortening of the metacarpal, metatarsal, and phalangeal bones, notably the distal phalanx of the thumb and the fourth metacarpal; and cone epiphyses. Occasionally, there may be radiographic evidence of hyperparathyroidism or osteomalacia.

Differential diagnosis. Hypocalcemia, hyperphosphatemia, and elevated levels of circulating PTH in the absence of renal disease, steatorrhea, and generalized osteomalacia are characteristic of PHP1. A diagnosis of PPHP may be difficult to establish in infancy, particularly when there is no family history of AHO. The differential diagnosis includes POH, congenital plate-like osteoma cutis, and familial osteoma cutis in families without evidence of AHO.⁹⁰

Treatment and prognosis. Treatment of PHP is directed towards controlling hypocalcemia by careful administration and monitoring of calcium and vitamin D. Normocalcemic patients must be monitored closely and evaluated regularly for the development of cataracts or hypocalcemia. Mental retardation may be causally related to poorly-controlled or undetected hypocalcemia. Patients should also be screened for hypothyroidism. There is no effective treatment for osteoma cutis. Surgical excision may be considered for individual lesions that cause pain or cosmetic disfigurement.

Progressive osseous heteroplasia

Progressive osseous heteroplasia (POH) is characterized by progressive heterotopic ossification of the skin and deeper soft tissues, including muscle.^{88,92,93} It presents at birth or in early infancy with focal areas of dermal ossification that enlarge and coalesce to form larger nodules and plaques. Extension to the subcutaneous tissues and muscle often results in ankylosis of affected joints and growth retardation of involved limbs. There have been case reports of ossification limited to one half of the body or to a single limb.^{93,94} Histopathologic examination reveals mainly intramembranous ossification similar to that seen in AHO, although foci of enchondral bone formation with cartilage are sometimes present. There is a female preponderance. POH may be sporadic or inherited as an autosomal dominant trait with phenotypic variability.⁹² Familial cases have been linked to *GNAS1* mutations inherited exclusively from the father.^{91,95}

POH is not associated with endocrine dysfunction or the skeletal and developmental abnormalities of Albright hereditary osteodystrophy. The heterotopic ossification in AHO is usually more superficial and limited to the dermis and subcutis. However, the clinical phenotype of POH is observed in families with AHO (Fig. 26.16).⁹⁶ The relationship of AHO to POH and other forms of osteoma cutis awaits further understanding of mutations in the *GNAS1* gene and their effects on osteogenic differentiation in the skin and soft tissues.⁹⁷

Congenital plate-like osteoma cutis

Congenital plate-like osteoma cutis (POC) is a rare entity that occurs in infants with no abnormality of calcium or phosphate metabolism.⁸⁹ Lesions present at birth or in the first year of life as a large, asymptomatic, skin-colored plaque, varying in size from 1–15 cm. There are no predisposing events such as trauma or infection to explain the heterotopic ossification. The scalp is the site of predilection, but lesions may also be found on the limbs or trunk. There are no associated abnormalities. Radiographs reveal calcified sheets or nodules in the subcutaneous soft tissues. Histopathology shows mature spongy bone in the dermis and subcutis. There may be gradual progression of the lesion with time and clinical overlap with POH. It is proposed that the term congenital plate-like osteoma cutis should be reserved for nonprogressive, superficial lesions to distinguish this disorder from POH in which ossification extends deeper into muscle and is relentlessly progressive.⁸⁸ *GNAS1* mutations have been reported suggesting it may be a variant of POH.⁸⁹ Treatment is by excision, if necessary and feasible. Recurrence after excision has been reported.

Pilomatricoma

Pilomatricoma, previously known as calcifying epithelioma of Malherbe, is a benign adnexal tumor derived from hair matrix cells. It commonly appears in children in the first decade of life and may be seen in infancy.^{98,99} Familial occurrence is documented and it can be associated with myotonic dystrophy or Gardner syndrome and familial adenomatous polyposis (FAP).^{100,101} There is a slight female preponderance.⁹⁹

Cutaneous findings. The pilomatricoma presents clinically as a slowly enlarging, hard nodule that is fixed to the skin but freely mobile over the underlying tissues. The overlying skin may be white, skin-colored, or have a blue-red discoloration. The size varies from 0.1–6 cm in diameter, with an average of about 1 cm.⁹⁹ Ulceration of the overlying skin occurs rarely, with discharge of a white chalk-like material, and rapid enlargement due to bleeding within the lesion has been described.¹⁰² Pilomatricomas are seen most commonly on the head and neck (Figs 26.17, 26.18), but also appear on the trunk and extremities (Fig. 26.19). They are usually solitary, but multiple and recurrent pilomatricomas are well recognized and may be seen



Figure 26.17 Pilomatricoma on the right cheek with slight bluish discoloration of the skin.



Figure 26.18 Skin-colored pilomatricoma on the right cheek.



Figure 26.19 Pilomatricomas on the arm.

in otherwise healthy children. Multiple lesions are reported in myotonic dystrophy, Gardners syndrome and FAP, the Rubinstein–Taybi, Soto and Turner syndromes and in association with trisomy 9, gliomatosis cerebri and glioblastoma.^{98,101,103–105}

Extracutaneous findings. Most patients with pilomatricoma have no extracutaneous findings. Myotonic dystrophy and a familial predisposition to adenomatous polyposis coli should be considered in children with multiple pilomatricomas.^{101–105}

Etiology and pathogenesis. The tumor derives from cells in the hair matrix. Mutations in the β -catenin gene, a gene associated with colon cancer, have been demonstrated in pilomatricomas.¹⁰⁶ Mutations in APC causative for Gardner syndrome/FAP may result in pilomatricoma formation possibly by affecting a different part of the same Wnt signaling pathway.¹⁰¹

Diagnosis. The histopathology of pilomatricoma is very characteristic, with two distinct types of cell, basophilic and shadow cells, located in the dermis or subcutis and surrounded by a fibrous capsule. The basophilic cells are seen at the periphery of the tumor and have rounded, darkly staining nuclei and scanty cytoplasm. The shadow cells are eosinophilic with a well-defined border and a central unstained area where the nucleus has been lost. Areas of keratinization may be seen, with



Figure 26.20 Subcutaneous granuloma annulare in a 19-month-old child.

foreign body giant cells and melanin pigmentation. Dystrophic calcification is a common finding and ossification occasionally occurs. Immunohistochemical staining typically shows nuclear β -catenin accumulation in the basaloid cellular component.¹⁰¹

Differential diagnosis. The clinical differential diagnosis includes other skin tumors, dermoid cyst, or a calcified nodule. Dermoid cysts are attached to underlying tissues rather than to the skin. A calcified nodule is hard to palpation and has a white surface discoloration; it can be difficult to distinguish clinically from a calcified pilomatricoma. Ultrasound examination of pilomatricomas shows a mass with an echogenic center and a hyperechoic rim at the junction of the dermis and subcutaneous fat.¹⁰⁷

Presentation with multiple lesions or familial disease should raise the possibility of an underlying genetic disorder.¹⁰¹

Treatment and prognosis. Surgical excision with narrow margins or through a small skin incision is the treatment of choice. In asymptomatic lesions without progressive growth or recurrent inflammation, this may be deferred until the child is older and able to cooperate with excision under local anesthesia. Very superficial lesions may be amenable to incision and curettage. Spontaneous resolution is occasionally observed.

Granuloma annulare

Granuloma annulare is a benign inflammatory skin disorder of unknown etiology. The typical morphology is of skin-colored, erythematous or violaceous dermal papules that extend with centrifugal clearing to form an annular lesion with a beaded margin. Other variants include: subcutaneous granuloma annulare (Fig. 26.20), which may resemble rheumatoid nodules; a generalized papular form, perforating granuloma annulare; and a patch type.¹⁰⁸

While not uncommon in school-aged children, granuloma annulare is rarely seen in infancy. A number of cases of generalized granuloma annulare have been reported in Korean children as young as 3 months of age.^{109,110} Two of these occurred following Bacille Calmette–Guérin (BCG) vaccination.¹⁰⁹ Subcutaneous granuloma annulare may occur in young children,

and a case of apparent congenital onset has been described.^{111,112} Granuloma annulare with a rare linear distribution developed in an infant at 8 months of age.¹¹³ Unusual presentations of granuloma annulare are confirmed by the histopathologic finding of palisading granulomas associated with areas of collagen degeneration and mucin deposition in the dermis.

Most cases resolve spontaneously and treatment is rarely necessary.

Hamartomas

A hamartoma is a developmental abnormality of the skin in which there is an excess of one or more mature or nearly mature tissue structures normally found at that site.¹¹⁴ The term nevus is often used synonymously, although not all ‘nevi’ are hamartomas (e.g., nevus anemicus, nevus depigmentosus). Whether a lesion is designated a hamartoma or a nevus depends largely on tradition. An organoid nevus or organoid hamartoma refers to a malformation that contains adnexal structures such as sebaceous glands or hair follicles.¹¹⁵

Most hamartomas are isolated, sporadic malformations. They can be single or multiple, localized or extensive, and may be distributed in a linear or whorled pattern corresponding to the lines of Blaschko. Some arise from a post-zygotic mutation in the embryo that leads to somatic mosaicism.¹¹⁶ Others are manifestations of well-defined genetic disorders such as tuberous sclerosis. Epidermal hamartomas may be associated with underlying abnormalities in the central nervous system, skeleton, or other organs. Rarely, a post-zygotic mutation that involves the germline results in transmission of generalized skin disease to subsequent offspring.^{116,117}

EPIDERMAL NEVUS

The term epidermal nevus is used to encompass a group of hamartomas of ectodermal origin in which there is clinical and histopathologic overlap (Box 26.2). These include the nevus sebaceus, linear keratinocytic epidermal nevus, inflammatory linear verrucous epidermal nevus (ILVEN), and nevus comedonicus. Other hamartomas that may be considered epidermal nevi are syringocystadenoma papilliferum, linear porokeratosis, Becker nevus, and the porokeratotic eccrine nevus (porokeratotic eccrine and ostial dermal duct nevus). Epidermal nevi also occur as a component of a number of well-defined

BOX 26.2 EPIDERMAL NEVI

ORGANOID NEVI

- Nevus sebaceus
- Syringocystadenoma papilliferum^a
- Nevus comedonicus
- Porokeratotic eccrine and ostial dermal duct nevus (porokeratotic eccrine nevus)
- Becker nevus

KERATINOCYTIC (NONORGANOID) NEVI

- Nonepidermolytic nevus
- Epidermolytic nevus
- Inflammatory linear verrucous epidermal nevus (ILVEN)
- Linear Cowden nevus
- Linear porokeratosis

^aOften occurs in association with a nevus sebaceus.

or less well-defined syndromes.^{115,118} When applied without qualification, the term epidermal nevus usually refers to a keratinocytic epidermal nevus. Epidermal nevi affect about 0.1–0.3% of newborns.¹¹⁹

NEVUS SEBACEUS

The nevus sebaceus (of Jadassohn) is an organoid hamartoma of appendageal structures and is present at birth. It occurs mainly where pilosebaceous and apocrine structures are prominent on the head and neck. There is no racial or gender predilection.

Cutaneous findings. The typical nevus sebaceus is a pink-yellow or yellow-orange plaque with a pebbly or velvety surface that is located on the scalp or face (Fig. 26.21). It varies in size from one to several centimeters and can be round, oval, or linear in shape. Lesions on the scalp present as a congenital area of circumscribed alopecia (Fig. 26.21B). There may be evolution from a slightly raised plaque at birth to a flat, almost macular lesion in infancy and childhood. A verrucous or cobblestone appearance develops in adolescence when the sebaceous and apocrine glands enlarge and proliferate.¹¹⁴ Some lesions present with an atypical cerebriform (Fig. 26.22) or papillomatous morphology (Fig. 26.23).

Extracutaneous findings. Nevus sebaceus is usually an isolated lesion with no extracutaneous findings. Rarely, it is associated with other developmental abnormalities in the Schimmelpenning or linear nevus sebaceus syndrome.¹¹⁵ The nevus sebaceus can be of any size or shape but is often extensive and/or linear, with a distribution following the lines of Blaschko. Extracutaneous manifestations include mental retardation, seizures and other central nervous system abnormalities, skeletal developmental anomalies, and ocular lesions, including coloboma of the eyelid and lipodermoid of the conjunctiva.^{115,117,120–122} Vitamin D-resistant hypophosphatemic rickets is a less common but well-described association.^{115,117,123,124} Vascular anomalies are also reported.¹²⁵

A related syndrome in which an extensive nevus sebaceus is associated with a large speckled lentiginous nevus (which appears as an area of segmental hyperpigmentation in infancy) is termed *phakomatosis pigmentokeratolica* (PPK) (see Chapter 24). Hypophosphatemic rickets occurs more commonly in PPK whereas ocular lipodermoids and colobomas are apparently not found.¹¹⁵ Nevus sebaceus adjacent to an area of aplasia cutis congenita has been termed *didymosis aplasticosebacea*, or SCALP syndrome when the additional features of CNS abnormalities, limbal dermoid and pigmented melanocytic nevus are present.¹²⁶

Etiology and pathogenesis. Nevus sebaceus is thought to be caused by a post-zygotic somatic gene mutation. Lesional mutations in *HRAS*, and less commonly *KRAS*, have been identified both in localized nevus sebaceus and in Schimmelpenning syndrome.^{119,127} There have been rare reports of familial occurrence of nevus sebaceus.^{128,129} The Schimmelpenning syndrome occurs sporadically, and an autosomal lethal mutation that survives by mosaicism is postulated.¹³⁰

Diagnosis. The diagnosis of nevus sebaceus is usually made on clinical grounds except in atypical cases. In infancy and childhood the characteristic histopathologic changes are less developed than in adolescence and adulthood. Mature lesions



Figure 26.23 Nevus sebaceus with a papillomatous appearance.

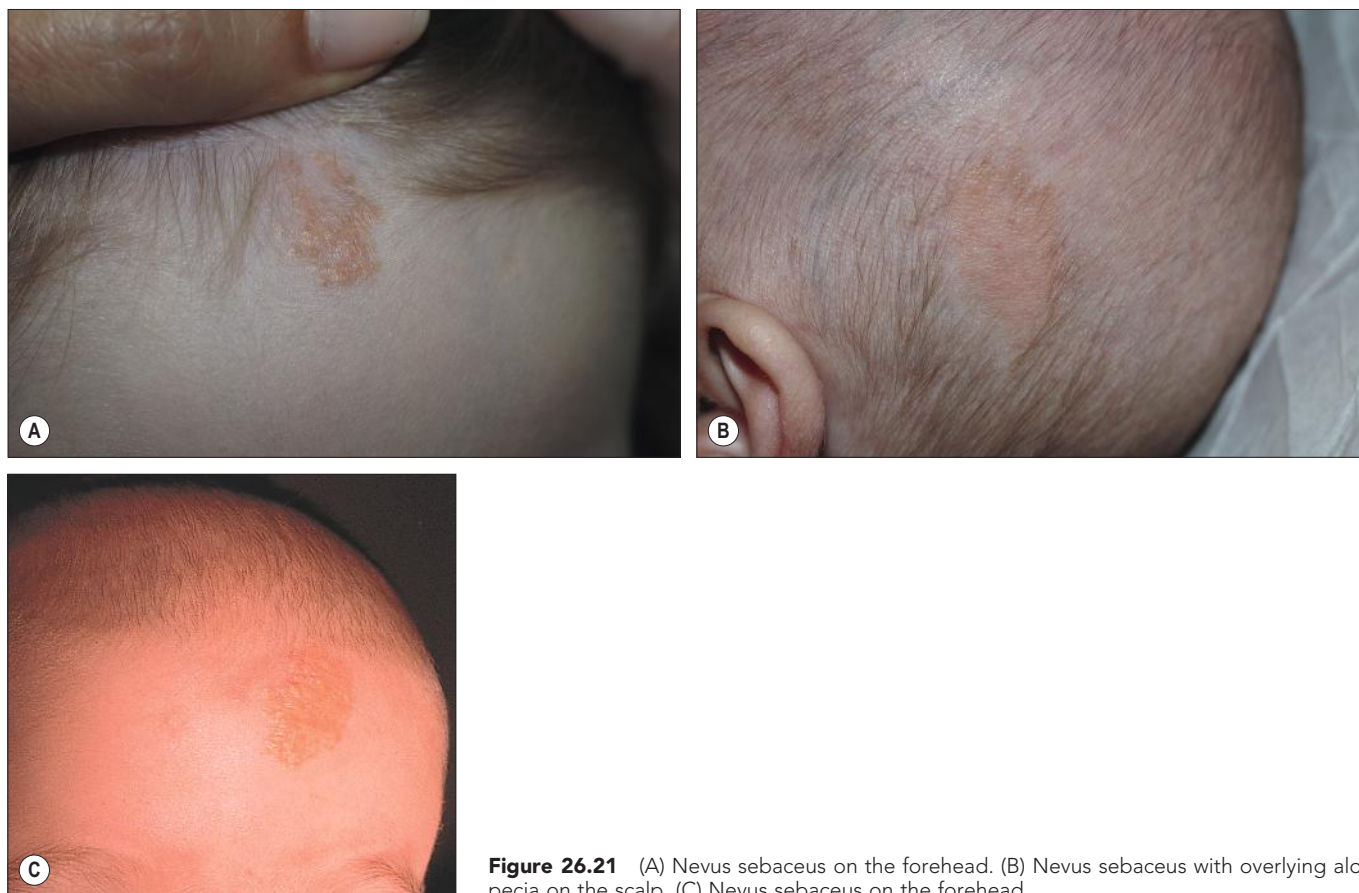


Figure 26.21 (A) Nevus sebaceus on the forehead. (B) Nevus sebaceus with overlying alopecia on the scalp. (C) Nevus sebaceus on the forehead.



Figure 26.22 Nevus sebaceus with cerebriform morphology on the scalp.

show numerous hyperplastic sebaceous and apocrine glands in the dermis, with overlying epidermal hyperplasia. In infants the histopathologic findings are more subtle, with rudimentary hair follicles and immature glandular structures. Sebaceous hyperplasia may not be so evident in a linear nevus sebaceus localized outside the head and neck area.¹¹⁵

Differential diagnosis. The differential diagnosis of a circumscribed area of alopecia on the scalp at birth includes aplasia cutis congenita and neural tube closure defects such as meningocele, encephalocele, and rests of heterotopic meningeal or brain tissue in the skin (see [Chapter 9](#)). Aplasia cutis congenita can be distinguished by the presence of atrophy and scarring, and in some cases ulceration of the skin at birth. Neural tube defects are located in or close to the midline at the vertex, nasal bridge, or lower occipital scalp. Both aplasia cutis congenita and neural tube closure defects may show a collarette of dark terminal hair in the newborn.¹³¹ Eczematous changes overlying a nevus sebaceus may sometimes cause diagnostic confusion.¹³²

Treatment and prognosis. The nevus sebaceus has a propensity to develop neoplastic growths, most of which are benign appendageal tumors such as syringocystadenoma papilliferum, trichilemmoma, trichoblastoma, and apocrine cystadenoma. Malignant tumors include basal cell epithelioma, squamous cell carcinoma, and apocrine or sebaceous carcinoma. These tumors are unusual in childhood, are localized to the skin lesion and rarely metastasize, although they may be locally invasive.¹³³ The lifetime risk of developing a superimposed malignant tumor is uncertain, and previously high figures may be due to ascertainment bias.¹³³ More recent studies have found a lower incidence of malignant tumors and suggest that benign follicular neoplasms such as trichoblastoma may have been misinterpreted as basal cell carcinoma in the past.^{134–136} Changes that should lead one to suspect a neoplastic growth include surface ulceration or the development of a nodule within the lesion.

The need for prophylactic excision of a nevus sebaceus is controversial.¹³⁴⁻¹³⁶ Decisions regarding surgery should be individualized. Excision may be performed in infancy or postponed until later childhood or adolescence. Continued observation may be preferable to surgery for lesions that are difficult to excise with a good cosmetic result, particularly on the face.

SYRINGOCYSTADENOMA PAPILLIFERUM

Syringocystadenoma papilliferum (SCAP) is a benign adnexal hamartoma believed to be derived from either apocrine and/or eccrine glands or pluripotential appendageal cells.¹³⁷ When it occurs *de novo*, it is typically congenital but some cases develop later in life. The clinical appearance is of one or more papules or papillomatous lesions arranged singly or in clusters, as a confluent plaque, or in a linear distribution. Papules may be skin colored, pink or light brown and there may be surface ulceration.¹³⁸ The scalp, face, and neck are the typical sites of predilection. However, lesions occur on the trunk and extremities in approximately 25% of cases and unusual presentations are described.¹³⁹ Development of SCAP in an 8-year-old child with focal dermal hypoplasia and a documented *PORCN* mutation is reported.¹⁴⁰

Syringocystadenoma papilliferum arises within a nevus sebaceus in at least 30% of cases.¹³⁹ It may also rarely be associated with other adnexal hamartomas such as apocrine cystadenoma, hidrocystoma and apocrine nevus. The diagnosis is made by histopathologic examination. This is characterized by cystic and epidermal invaginations with papillary projections lined by an outer layer of cuboidal cells and an inner layer of columnar cells; a connective tissue core contains plasma cells and lymphocytes.

Surgical excision is the treatment of choice. Ablation with the CO₂ laser has been described in a newborn.¹⁴¹ There are rare reports of syringocystadenocarcinoma papilliferum arising from SCAP in older adults.¹⁴²

KERATINOCYTIC EPIDERMAL NEVUS

The keratinocytic epidermal nevus is a nonorganoid hamartoma of keratinocytes that may present at birth, within the first few years of life, or sometimes later.¹¹⁷ There are a number of histopathologic variants including nonepidermolytic, epidermolytic and inflammatory linear epidermal nevus subtypes.¹¹⁷

Cutaneous findings. The keratinocytic epidermal nevus presents at birth or during early childhood and may continue to extend for a variable period.¹¹⁷ Rarely, new lesions become apparent in adolescence or adult life. They vary in extent from a small cluster or linear arrangement of pigmented, warty papules to widespread linear and swirled areas of pigmentation following the lines of Blaschko (Fig. 26.24A,B). A linear keratinocytic nevus may involve an entire limb, half of the body in a unilateral distribution, or both sides of the trunk, limbs, and face in a symmetric pattern, with demarcation at the midline. Extensive bilateral lesions have been referred to historically as ‘systematized epidermal nevus’ or ‘ichthyosis hystrix,’ and unilateral lesions as ‘nevus unius lateris.’

Keratinocytic nevi may have a macerated appearance at birth because of prolonged contact with amniotic fluid (Fig. 26.24C). During childhood, the degree of verrucosity varies from subtle, almost flat pigmentation to a grossly elevated, warty appearance.¹¹⁷ They have a tendency to become more

verrucous with age, particularly during puberty. Keratinocytic nevi involving the head and neck often exhibit the morphology of a nevus sebaceus. Scalp lesions may be associated with woolly hair nevus, and occasional epidermal nevi have overlying hypertrichosis.¹⁴³ A linear lesion that impinges on the nail matrix may cause dystrophy of the involved nail.

A number of patients with one or more small hyperkeratotic papules with a distinctive histopathologic appearance have been described as ‘papular epidermal nevus with skyline basal cell layer’ or PENS.¹⁴⁴ Somewhat similar epidermal nevi with a white color have been observed at birth as a presentation of tuberous sclerosis.¹⁴⁵

The linear inflammatory verrucous epidermal nevus (ILVEN) is an extremely pruritic, erythematous lesion that can occur at any site, but is most often seen on the limbs or perineum in girls (Fig. 26.25). It may simulate linear psoriasis or linear lichen planus. It is rarely present at birth, but may appear in the first months of life.

Extracutaneous findings. Most keratinocytic nevi are isolated lesions with no evidence of extracutaneous disease. A number of syndromes are associated with non-epidermolytic keratinocytic nevi.^{115,118} These include Proteus syndrome; CLOVES (congenital lipomatous overgrowth, vascular malformation, epidermal nevus and skeletal abnormalities) syndrome; type 2 segmental Cowden disease; FGFR3 epidermal nevus, and CHILD (congenital hemidysplasia with ichthyosiform nevus and limb defects) syndrome.^{115,118} In the Proteus syndrome, epidermal nevi occur in association with limb overgrowth, lipomatous lesions, cerebriform malformations of the feet, and cutaneous vascular anomalies.^{106,117} The CHILD syndrome is characterized by verrucous lesions corresponding to the lines of Blaschko in conjunction with limb reduction defects.^{117,130}

Extracutaneous manifestations have also been described in association with PENS.^{146,147}

Diagnosis. The most common histopathologic pattern is that of a benign papilloma, with acanthosis, elongation of rete ridges, hyperkeratosis, and papillomatosis. This histopathologic appearance may be shared by viral warts, seborrheic keratosis, or acanthosis nigricans. Histopathology of lesions from the scalp may reveal features of a nevus sebaceus, especially after puberty. A subset of keratinocytic nevi shows the histopathologic features of epidermolytic hyperkeratosis, characterized by perinuclear vacuolization of keratinocytes and increased numbers of enlarged keratohyalin granules with overlying hyperkeratosis. In a less common variant, there is acantholytic hyperkeratosis similar to that seen in Darier disease.¹⁴⁸ Another rare variant is linear Cowden nevus, described as having a soft, thick papillomatous appearance and associated with a PTEN mutation.¹¹⁵ In PENS, the basal cell nuclei have a characteristic palisaded pattern.¹⁴⁴ Histopathologic findings in ILVEN include psoriasiform epidermal hyperplasia and an inflammatory infiltrate in the upper dermis.¹¹⁷ The nevus of CHILD syndrome resembles ILVEN but may also have collections of foam cells in the upper dermis consistent with a verruciform xanthoma.¹¹⁷

Etiology and pathogenesis. The distribution of lesions following the lines of Blaschko suggests somatic mosaicism. Chromosomal mosaicism has been demonstrated in a number of patients with linear keratinocytic nevi.^{149,150} Keratin 1 and 10 gene mutations have been identified in epidermolytic keratinocytic nevi.¹⁵¹ Keratinocytic nevi are thought to represent a



Figure 26.24 Linear keratinocytic nevus following the lines of Blaschko on (A) shoulder and arm, and (B) the trunk. (C) Keratinocytic nevus on the leg shortly after delivery.



Figure 26.25 Inflammatory linear epidermal nevus (ILVEN) on dorsal hand and finger.

phenotypic expression of several genetic defects due to post-zygotic mutations, rather than a single disease. Whether the basic pathogenetic defect of nonepidermolytic lesions lies in the dermal fibroblast or in the keratinocyte is not known.

Differential diagnosis. The differential diagnosis of a localized cluster of lesions includes viral warts, which do not commonly have a linear arrangement and regress spontaneously with time. Linear lesions at birth may be confused with the verrucous stage of incontinentia pigmenti. Linear keratinocytic nevi that develop during infancy and childhood differ in morphology, if not in distribution, from lichen striatus, a self-limiting disorder with an inflammatory, papular appearance and lichenoid histopathology. The differential diagnosis of ILVEN includes lichen simplex chronicus, linear psoriasis, and linear lichen planus, none of which is seen in the newborn period.

The CHILD syndrome, the CLOVE syndrome and Proteus syndrome have distinctive clinical features.

Treatment and prognosis. Unlike nevus sebaceus, the linear keratinocytic nevus is rarely associated with the development of superimposed benign or malignant tumors in adult life. Patients with epidermal nevi should be evaluated clinically for manifestations of one of the epidermal nevus syndromes.^{115,118} When histopathologic examination shows epidermolytic hyperkeratosis, the patient should receive counseling about the potential for genetic transmission of a keratinopathic ichthyosis via germline mutation although the actual risk of transmission is not known.

Treatment may be requested for cosmetically disfiguring lesions but is generally undertaken in later childhood or adolescence. Excision of small lesions or localized areas of larger lesions may be feasible. Treatment of extensive nevi is difficult. Various destructive modalities, including CO₂ laser ablation, dermabrasion, or liquid nitrogen cryotherapy, have been attempted, but there may be recurrence.¹¹⁷ The same is true for pharmacologic treatments such as topical or oral retinoids and 5-fluorouracil.¹⁵²

NEVUS COMEDONICUS

A nevus comedonicus is a developmental abnormality of the pilosebaceous unit that appears as a grouped or linear arrangement of small or large comedones. Lesions present at birth or during infancy in the majority of cases. Nevus comedonicus is considered a rare type of epidermal nevus.

Cutaneous findings. Groups of enlarged follicular openings containing pigmented, comedo-like keratin plugs may be localized or extensive (Fig 26.26). Most nevi are unilateral and located on the face or upper trunk. They frequently have a linear arrangement. Extensive lesions are distributed along the lines of Blaschko and are limited at the midline.^{153,144} There may be associated white papules representing milia, closed comedones, or deeper follicular cystic structures. Interfollicular atrophy is often observed.¹¹⁵

Later in childhood or adolescence these lesions may develop painful, inflammatory cystic nodules and acneiform scarring (Fig. 26.26).¹⁵⁴ The coexistence of a nevus comedonicus and a keratinocytic epidermal nevus has been reported.¹⁵⁵ Comedo-like structures may also be seen within keratinocytic nevi.¹¹⁷



Figure 26.26 Comedones, inflammatory and noninflammatory cysts in an adolescent.

Extracutaneous findings. In most cases, there are no extracutaneous manifestations. Rarely, a nevus comedonicus is associated with ipsilateral central nervous system, skeletal, and ocular abnormalities in the nevus comedonicus syndrome.¹¹⁵ Ipsilateral cataracts are a characteristic feature.¹¹⁵ Rarely, these extracutaneous anomalies may be localized contralaterally.¹¹⁵

Etiology and pathogenesis. Nevus comedonicus is a sporadic disorder and is not inherited. The pathogenesis is believed to involve somatic mosaicism.^{130,156} A mutation in the fibroblast growth factor receptor 2 (*FGFR2*) gene detected in an inflammatory acne nevus suggests that some cases of this type of nevus represent a mosaic form of Apert syndrome.¹⁵⁷

Diagnosis. The diagnosis is made on the clinical appearance of the lesion. Histopathologic examination reveals hyperkeratosis and acanthosis of the epidermis with widely dilated, keratin-filled, cystic structures. Epidermolytic hyperkeratosis may be observed in the keratinocytes of the follicular epithelial wall.^{153,154}

Differential diagnosis. The localized appearance of the lesion is very characteristic and unlikely to be mistaken for comedonal acne unless bilateral.¹⁵⁶

Porokeratotic eccrine nevus presents with comedo-like lesions on the palms and soles and has distinctive histopathologic features.

Inflammatory cysts may closely resemble cystic acne.

Nevus comedonicus syndrome should be distinguished from the Happle–Tinschert syndrome, in which multiple segmentally arranged basaloid follicular hamartomas are associated with ipsilateral osseous, dental and cerebral anomalies, and from a less well-defined syndrome with multiple trichilemmal cysts arranged along Blaschko's lines.^{115,118,158}

Treatment and prognosis. Recurrent inflammation and scarring can cause cosmetic disfigurement. Treatment is difficult. Excision of smaller lesions is curative,¹⁵⁹ but inflammatory acneiform cysts may recur if excision is incomplete. Pharmacologic agents such as oral or topical retinoids are of minimal benefit. Topical and systemic antibiotics have been used to treat inflammatory lesions, with variable success.¹⁵⁶

POROKERATOTIC ECCRINE NEVUS

The porokeratotic eccrine nevus is a congenital hamartoma of the eccrine ducts and follicular openings. Although usually present at birth, lesions may first appear in later childhood or adult life. Other terms used to describe this hamartoma include porokeratotic eccrine ostial and dermal duct nevus, porokeratotic eccrine and hair follicle nevus and porokeratotic adnexal ostial nevus.¹⁶⁰

Cutaneous and extracutaneous findings. Porokeratotic eccrine nevus is characterized clinically by grouped comedo-like keratotic papules or pits on a palm or sole.¹⁶¹ Lesions may be more widespread with a linear distribution following the lines of Blaschko.¹⁶² Keratotic papules and plaques located in sites other than the palms and soles may resemble a linear keratinocytic nevus or ILVEN.^{162,163} Multiple erosions and atrophy have been reported in cases presenting in the newborn period.¹⁶⁰ Most cases are asymptomatic but pruritus has been

reported.¹⁶⁰ Rare cases have associated anhidrosis, hair loss and nail dysplasia, psoriasis, palmar plantar keratoderma or ipsilateral breast hypoplasia.¹⁶⁰ Development of Bowen disease or squamous cell carcinoma within the lesional skin is an unusual complication.¹⁶⁰

Cases of generalized porokeratotic eccrine nevus associated with deafness and also with the keratitis-ichthyosis-deafness (KID) syndrome have been reported.^{164–166}

Etiology and pathogenesis. The pathogenesis is believed to represent a circumscribed disorder of keratinization localized to the acrosyringium and follicular ostia.¹⁶² Somatic mutations in the *GJB2* gene encoding the gap junction protein connexin 26, have been identified in patients with generalized porokeratotic eccrine nevus suggesting it might be a mosaic form of the KID syndrome.¹⁶⁶ These authors also report the observation of generalized lethal KID syndrome in an infant born to a mother with porokeratotic eccrine nevus.

Diagnosis. Histopathologically, there are epidermal invaginations with parakeratotic plugs emerging from dilated eccrine ostia and follicular openings, surrounded by parakeratotic columns of cornoid lamellae.¹⁶⁰

Differential diagnosis. The clinical differential diagnosis includes linear porokeratosis, nevus comedonicus, and linear keratinocytic nevus. Histopathologically, punctate porokeratosis and linear porokeratosis of Mibelli can be distinguished by the lack of epidermal invaginations. The histopathologic features can resemble those seen in KID syndrome.¹⁶⁶

Treatment and prognosis. Treatment is unsatisfactory.¹⁶⁰ There are reports of successful treatment with the ultrapulsed CO₂ laser but recurrence has been noted.^{160,162,167}

CONGENITAL SMOOTH MUSCLE HAMARTOMA

Congenital smooth muscle hamartoma is a benign cutaneous developmental anomaly characterized by an excess of arrector pili muscle within the reticular dermis. It is usually evident at birth or shortly thereafter. The estimated prevalence is 1 in 2600 live births, with a slight male preponderance.¹⁶⁸ Rarely, more extensive involvement may be associated with the phenotype of the ‘Michelin tire baby’.^{169–172}

Cutaneous findings. The typical congenital smooth muscle hamartoma presents as a lightly pigmented plaque or patch with overlying hypertrichosis (Fig. 26.27). The trunk, in particular the lumbosacral area, is the site of predilection, but lesions may also occur on the proximal limbs. Perifollicular papules are sometimes evident.¹⁷³ The overlying hair is vellus in type. Hypertrichosis is not invariable, and the hamartoma may present as a plaque of perifollicular papules with little or no increase in hair growth.¹⁷⁴ Transient elevation or a rippling movement of the lesion due to contraction of the muscle bundles can sometimes be elicited by rubbing or stroking the surface. Rarely, a congenital smooth muscle hamartoma has a linear configuration, or presents with multiple lesions or diffuse involvement.^{172,175,176}

Extracutaneous findings. There are no systemic findings with localized lesions. There may be associated growth and developmental abnormalities in children with extensive smooth



Figure 26.27 Congenital smooth muscle hamartoma, with close-up view.

muscle hamartoma as a manifestation of the ‘Michelin tire baby’ syndrome.^{171,172} Unilateral hypoplasia of the breast and other cutaneous, muscular, or skeletal defects may be associated with smooth muscle hamartoma in the Becker nevus syndrome.¹⁷⁷

Etiology and pathogenesis. Congenital smooth muscle hamartoma is believed to represent aberrant development of pilar smooth muscle during fetal life. It has been suggested that the hamartoma involves other structures, such as neural tissue and hair.¹⁷³ The hypertrichosis appears to result from increased hair length and diameter rather than an increase in hair density.¹⁷⁴

Diagnosis. Light microscopic examination of a skin biopsy specimen will establish the diagnosis if the clinical appearance is atypical. Numerous well-defined and variably oriented bundles of smooth muscle are seen within the reticular dermis. They may or may not be associated with follicular structures. Increased epidermal pigmentation may be observed.

Differential diagnosis. The differential diagnosis of congenital smooth muscle hamartoma includes Becker nevus, nevus pilosus, leiomyoma, connective tissue nevus, solitary mastocytoma, plexiform neurofibroma, and a congenital hairy melanocytic nevus. Smooth muscle may be observed in the dermis in Becker nevus, and a continuum between the two conditions has been proposed.¹⁷³ Unlike Becker nevus, the congenital smooth muscle hamartoma is always present at birth, does not show prominent epidermal changes, and may demonstrate abnormally whorled myofilaments on electron microscopy.¹⁷⁴

A nevus pilosus, or hairy patch, shows no alteration in skin texture or pigmentation, and the hair is usually terminal in type. A congenital melanocytic nevus is more deeply pigmented, and the overlying hypertrichosis is composed of terminal hair. Leiomyoma is a circumscribed spindle-cell tumor. Connective tissue nevi and mastocytoma may be distinguished by skin biopsy.¹⁷⁴

Prognosis. This hamartoma has no malignant potential and the prognosis is excellent. There is a tendency for the pigmentation and hair growth to become less noticeable with age.¹⁶⁸

Treatment is unnecessary, unless there are cosmetic concerns in later life.

CONGENITAL BECKER NEVUS AND BECKER NEVUS SYNDROME

Becker nevus is an organoid hamartoma characterized by a circumscribed segmental area of hyperpigmentation and hypertrichosis. It is commonly located over the shoulder, chest, or scapula, and has a predilection for males. Although it is usually acquired in adolescence, a number of congenital cases of Becker nevus have been described.^{177–180} Histopathologic examination reveals acanthosis and hyperpigmentation of the basal layer of the epidermis, as well as a variable dermal component consisting of smooth muscle bundles that resemble congenital smooth muscle hamartoma.

The Becker nevus syndrome refers to an association with unilateral hypoplasia of the female breast and ipsilateral skeletal defects such as hypoplasia of the shoulder girdle or arm. Other reported anomalies include supernumerary nipples, scoliosis, spina bifida occulta, congenital adrenal hyperplasia, and accessory scrotum.^{115,177,179,181} The syndrome is twice as common in females, possibly because ipsilateral hypoplasia of the breast is easily recognized and reported.¹⁷⁷ A post-zygotic mutation that gives rise to mosaicism may explain the location of the nevus and associated anomalies in a similar body region.¹⁷⁷ Although both the isolated nevus and the Becker nevus syndrome are generally sporadic, there have been a few reports of familial aggregation.^{177,178} This phenomenon may be explained by param-dominant inheritance.^{117,182}

MICHELIN TIRE BABY

The term ‘Michelin tire baby’ describes numerous congenital transverse skin folds on all four limbs. These circumferential creases may be associated with an underlying diffuse nevus lipomatosus, smooth muscle hamartoma, or normal skin.^{170,183} There are several reports of familial cases.^{171,183,184} When associated with an underlying smooth muscle hamartoma there is often diffuse hyperpigmentation and hypertrichosis. The skin folds diminish slowly as the child grows.¹⁸³ The ‘Michelin tire baby syndrome’ refers to associated congenital anomalies, such as mental retardation, microcephaly, hemiplegia, hemihypertrophy, and chromosomal defects, suggesting a contiguous gene syndrome.^{171,172} Circumferential skin creases with associated anomalies have also been described as HITCH (hearing impairment, undescended testes, circumferential skin creases, and mental handicap) syndrome, MR/MCA (mental retardation, multiple congenital anomalies) syndrome, and ‘circumferential skin creases Kunze type’, denoting cleft palate, typical face, intellectual disability and growth delay.¹⁸⁵

NEVUS LIPOMATOSUS

Nevus lipomatosus cutaneus superficialis is a hamartoma composed of mature fat. Clinically, these lesions present at birth or later in childhood as an asymptomatic, soft or rubbery plaque with a polypoid or cerebriform appearance.¹⁸⁶ A linear arrangement of flesh-colored to yellow lesions in a zosteriform pattern is the most common presentation (Fig. 26.28). They are frequently observed in the lumbosacral or perineal areas, but can be located elsewhere. Although asymptomatic, a nevus



Figure 26.28 Nevus lipomatosus with soft polypoid nodules on the lower back.

lipomatosus may require excision for cosmetic reasons. Histopathology shows mature unencapsulated adipose tissue infiltrating between collagen bundles in the superficial and deep dermis.

A lipomatous lesion on the scalp with hair loss in a patient with encephalocraniocutaneous lipomatosis is termed *nevus psiloliparus*.¹⁸⁷ Fat herniations are seen in focal dermal hypoplasia (Goltz syndrome), and benign fat herniations may be observed on the feet of healthy infants.

CONNECTIVE TISSUE NEVUS

A connective tissue nevus is characterized by excessive deposition of one or more components of dermal connective tissue (collagen, elastin or glycosaminoglycans).^{188,189} These hamartomas may occur sporadically, or as a familial disorder with autosomal dominant transmission.¹⁸⁸ Connective tissue nevi are also seen as a manifestation of genetic syndromes, notably the ‘shagreen patch’ or collagenoma in tuberous sclerosis, and the multiple elastic tissue nevi of Buschke–Ollendorff syndrome.¹⁹⁰ A connective tissue nevus may be present at birth, but most become evident during childhood or adolescence.

Cutaneous findings. Connective tissue nevi present clinically as asymptomatic, firm, skin-colored to yellowish nodules or plaques located on the trunk or limbs (Fig. 26.29). The surface of the lesion may be smooth or have a ‘cobblestone,’ ‘leather-grain,’ or ‘peau d’orange’ appearance. They may be solitary or multiple. A linear or ‘zosteriform’ morphology is sometimes observed. A rare monomelic variant simulating linear scleroderma and causing functional impairment has been described in three children, with onset at birth or in early childhood.¹⁸⁹

Extracutaneous findings. Osteopoikilosis is seen in association with elastic tissue nevi in the Buschke–Ollendorff syndrome.¹⁹⁰ The skin lesions in this condition may rarely be present at birth, but the distinctive bone changes are not reported in infancy. The collagenoma or ‘shagreen patch’ of tuberous sclerosis develops in later childhood, although other stigmata of the disease may be present at birth or in early infancy. Cardiomyopathy may occur in association with the multiple lesions of familial cutaneous collagenoma and with



Figure 26.29 Flesh-colored nodules of connective tissue nevi on the back.

collagenomas and hypogonadism.¹⁸⁸ A cerebriform collagenoma on the sole of the foot may be an isolated phenomenon or a component of Proteus syndrome.¹⁹¹

Etiology and pathogenesis. The pathogenesis is unknown. In familial cutaneous collagenoma, the skin lesions are inherited as an autosomal dominant trait. Tuberous sclerosis and Buschke–Ollendorff syndrome are also inherited by autosomal dominant transmission; mutations in the *LEMD3* gene have been identified in Buschke–Ollendorff syndrome.¹⁸⁹ Somatic mosaicism may be postulated for sporadic lesions, particularly those with a linear distribution.

Diagnosis. Histopathologic examination of connective tissue nevi shows an excess of collagen or elastic tissue, or both, in the dermis. This excess may not be apparent unless a specimen of normal adjacent skin is obtained for comparison. Thus biopsies of connective tissue nevi are often reported as ‘normal skin.’ Special elastic stains are necessary to demonstrate the increased numbers of elastic fibers in elastic tissue nevi. A more uncommon cellular histopathologic variant has recently been identified.¹⁸⁹ Congenital mucinous nevus may be a variant of connective tissue nevus in which deposition of mucin (proteoglycan) in the dermis is the predominant histopathologic finding.¹⁹²

Differential diagnosis. The differential diagnosis includes other cutaneous hamartomas, such as neurofibroma, leiomyoma, smooth muscle hamartoma, and epidermal nevus. These entities may be distinguished by histopathologic examination of a skin biopsy specimen.

Treatment and prognosis. Connective tissue nevi are permanent lesions. They grow in proportion to the child’s growth. There is no malignant potential and most do not require treatment. Surgical excision may occasionally be indicated for cosmetic reasons.

PLAQUE-LIKE MYOFIBROBLASTIC TUMOR

The term plaque-like myofibroblastic tumor describes a rare, slowly enlarging, highly cellular spindle cell tumor observed in infancy or early childhood.^{193,194} It appears to have a



Figure 26.30 Acquired raised band on the leg of a young infant.


predilection for the back and hip area and may ulcerate.¹⁹⁴ Histopathology shows well-demarcated proliferation of spindle cells involving the entire reticular dermis and upper subcutis. The cells are immunoreactive for Factor VIII antigen and smooth muscle actin and negative for CD34. The tumor extends locally and complete excision appears to be curative.

Although the histopathologic features of this tumor resemble a dermatofibroma, it can be distinguished clinically by the young age of onset, large size and plaque-like morphology. The differential diagnosis of dermal neoplasms showing a fibroblastic/myofibroblastic line of differentiation also includes dermatomyofibroma, dermatofibrosarcoma protuberans, atypical fibroxanthoma, plexiform fibrohistiocytic tumor, infantile myofibroma, intradermal nodular fasciitis and fibroblastic connective tissue nevus (FCTN).¹⁹⁵ In contrast to plaque-like myofibroblastic tumor, FCTN stains positively for CD34; it is thought to most likely represent a localized and entirely benign developmental dermal anomaly.¹⁹⁵

Acquired raised bands of infancy

Acquired raised bands of infancy, also known as ‘raised limb bands’ were first reported by Meggitt and colleagues in 2002.¹⁹⁶ Since then, several other cases have been reported in a relatively short period, suggesting that the condition may not be rare. Onset is typically within the first few weeks to months of life. The lesions are flesh-colored linear bands, which are typically horizontally oriented, slightly firm, and elevated above the skin surface. Linear atrophic skin lesions may also be present.¹⁹⁷ Most have been located on the extremities (Fig. 26.30), but the torso can also be involved. A relationship to amniotic bands has been proposed but is debatable. At least one familial case has been reported. Although some cases have occurred in premature infants with a perinatal history of placental abruption, they are also described in healthy term infants.¹⁹⁸ Limited information about the natural history suggests that the number of bands stabilizes in infancy, and these asymptomatic lesions persist.

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Figures 8, 11, 12, 15, 16 and 23 are available online at ExpertConsult.com 

REFERENCES

- Coffin CM, Alaggio R. Fibromyoblastic and myofibroblastic tumors in children and adolescents. *Pediatr Dev Pathol* 2012;15(Suppl. 1): 127–80.
- Weiss SW, Goldblum JR. Fibromatoses. In: Enzinger and Weiss's soft tissue tumors. 5th ed. St Louis: Mosby; 2008. p. 237–56.
- Chung EB, Enzinger FM. Infantile myofibromatosis. *Cancer* 1981;48:1807–18.
- Stanford D, Rogers M. Dermatological presentations of infantile myofibromatosis: a review of 27 cases. *Aust J Dermatol* 2000;41:156–61.
- Brill PW, Yandow DR, Langer LO, et al. Congenital generalized fibromatosis. Case report and literature review. *Pediatr Radiol* 1982;12: 269–78.
- Parker RK, Mallory SB, Baker GF. Infantile myofibromatosis. *Pediatr Dermatol* 1991;8: 129–32.
- Goldberg NS, Bauer BS, Kraus H, et al. Infantile myofibromatosis: A review of clinicopathology with perspectives on new treatment choices. *Pediatr Dermatol* 1988;5:37–46.
- Buonuomo PS, Ruggiero A, Zampino G, et al. A newborn with multiple fractures as first presentation of infantile myofibromatosis. *J Perinatol* 2006;26:653–5.
- Kim EJ, Wang KC, Lee JY, et al. Congenital solitary infantile myofibromatosis involving the spinal cord. *J Neurosurg Pediatr* 2013;11(1): 82–6.
- Mynatt CJ, Feldman KA, Thompson LD. Orbital infantile myofibroma: a case report and clinicopathologic review of 24 cases from the literature. *Head Neck Pathol* 2011;5: 205–15.
- Wiswell TE, Sakas EL, Stephenson SR, et al. Infantile myofibromatosis. *Pediatrics* 1985;76: 981–4.
- Brasseur B, Chantrain CF, Godefroid N, et al. Development of renal and iliac aneurysms in a child with generalized infantile myofibromatosis. *Pediatr Nephrol* 2010;25:983–6.
- Smith A, Orchard D. Infantile myofibromatosis: two families supporting autosomal dominant inheritance. *Australas J Dermatol* 2011;52: 214–17.
- Levine E, Freneaux P, Schleiermacher G, et al. Risk-adapted therapy for infantile myofibromatosis in children. *Pediatr Blood Cancer* 2012;59:115–20.
- Keltz M, DiCostanzo D, Desai P, et al. Infantile (Desmoid-type) fibromatosis. *Pediatr Dermatol* 1995;12:149–51.
- Martinez-Lage JF, Acosta J, Sola J, et al. Congenital desmoid tumor of the scalp: a histologically benign lesion with aggressive clinical behavior. *Childs Nerv Syst* 1996;12:409–12.
- Pereyo NG, Heimer WL. Extraabdominal desmoid tumor. *J Am Acad Dermatol* 1996;34: 352–6.
- Faulkner LB, Hajdu SI, Kher U, et al. Pediatric desmoid tumor: Retrospective analysis of 63 cases. *J Clin Oncol* 1995;13:2813–18.
- Lachner H, Urban C, Benesch M, et al. Multimodal treatment of children with unresectable or recurrent desmoid tumors; An 11-year longitudinal observational study. *J Pediatr Hematol Oncol* 2004;26:518–22.
- Fotiadi C, Tsekouras DK, Antonakis P, et al. Gardner's syndrome: A case report and review of the literature. *World J Gastroenterol* 2005; 11:5408–11.
- Dormans JP, Spiegel D, Meyer J, et al. Fibromatoses in childhood: The desmoid/fibromatosis complex. *Med Pediatr Oncol* 2001;37:126–31.
- Wang W-L, Nero C, Pappo A, et al. CTNNB1 genotyping and APC screening in pediatric desmoid tumors: a proposed algorithm. *Pediatr Dev Pathol* 2012;15:361–7.
- Buitendijk A, van de Ven C, Dumans TG, et al. Pediatric aggressive fibromatosis: A retrospective analysis of 13 patients and review of the literature. *Cancer* 2005;104:1090–9.
- Skapek SX, Hawk BJ, Hoffer FA, et al. Combination chemotherapy using vinblastine and methotrexate for the treatment of progressive desmoid tumor in children. *J Clin Oncol* 1998; 16:3021–7.
- Eich GF, Hoeffel JC, Tschappeler H, et al. Fibrous tumors in children: imaging features of a heterogeneous group of disorders. *Pediatr Radiol* 1998;28:500–9.
- Cheng JCY, Tang SP, Chen TMK. Sternocleidomastoid pseudotumor and congenital muscular torticollis in infants: a prospective study of 510 cases. *J Pediatr* 1999;134:712–16.
- Niamba P, Leaute-Labreze C, Boralevi F, et al. Further documentation of spontaneous regression of infantile digital fibromatosis. *Pediatr Dermatol* 2007;24:280–4.
- Albertini JG, Welsch MJ, Conger LA, et al. Infantile digital fibroma treated with Mohs micrographic surgery. *Dermatol Surg* 2002;10: 959–61.
- Oh CK, Son HS, Kwon YW, et al. Intralesional fluorouracil injection in infantile digital fibromatosis. *Arch Dermatol* 2005;141:549–50.
- Paller AS, Gonzalez-Crussi, Sherman JO. Fibrous hamartoma of infancy. *Arch Dermatol* 1989;125:88–91.
- Dickey GE, Sotelo-Avila C. Fibrous hamartoma of infancy: current review. *Pediatr Dev Pathol* 1999;2:236–43.
- Fetsch JF, Miettinen M, Laskin WB, et al. A clinicopathological study of 45 pediatric soft tissue tumors with an admixture of adipose tissue and fibroblastic elements, and a proposal for classification as lipofibromatosis. *Am J Surg Pathol* 2000;24:1491–500.
- Chacon-Camacho OF, Vazquez JV, Zenteno JC. Expanding the phenotype of gingival hyperplasia – mental retardation – hypertrichosis (Zimmerman-Laband) syndrome. *Am J Med Genet* 2011;Part A 155:1716–20.
- Hart TC, Zhang Y, Gorry MC, et al. A mutation in the SOS1 gene causes hereditary gingival fibromatosis type 1. *Am J Hum Genet* 2002;70: 943–54.
- Ye X, Shi L, Cheng Y, et al. A novel locus for autosomal dominant hereditary gingival fibromatosis, GINGF3, maps to chromosome 2p22.3–p23.3. *Clin Genet* 2005;68:239–44.
- Tagaki M, Yamamoto H, Mega H, et al. Heterogeneity in the gingival fibromatoses. *Cancer* 1991;68:2202–12.
- O'Shea PA. Myogenic tumors of soft tissue. In: Coffin CM, Dehner LP, O'Shea PA, editors. *Pediatric soft tissue tumors: a clinical, pathological, and therapeutic approach*. Philadelphia: Williams & Wilkins; 1997. p. 214–53.
- Robati RM, Barikbin B, Kavand S, et al. Solitary cutaneous leiomyoma in an infant. *Pediatr Dermatol* 2009;26:621–3.
- Lupton GP, Naik DG, Rodman OG. An unusual congenital leiomyoma. *Pediatr Dermatol* 1986;3:158–60.
- Henderson CA, Ruban A, Porter DL. Multiple leiomyomata presenting in a child. *Pediatr Dermatol* 1997;14:287–9.
- Yang SS, Williams RJ, Bear BJ, et al. Leiomyoma of the hand in a child who has the human immunodeficiency virus: A case report. *J Bone Joint Surg Am* 1996;78-A:1904–6.
- McClatchey A. Neurofibromatosis. *Annu Rev Pathol* 2007;2:191–216.
- McCormack K, Kaplan D, Murray JC, et al. Multiple hairy pacinian neurofibromas (nerve-sheath myxomas). *J Am Acad Dermatol* 1988; 18:416–19.
- Caputo R, Ermacora E, Gelmetti C, et al. Generalized eruptive histiocytoma in children. *J Am Acad Dermatol* 1987;17:449–54.
- Jang KA, Lee HJ, Choi JH, et al. Generalized eruptive histiocytoma of childhood. *Br J Dermatol* 1999;140:174–6.
- Hernandez-Martin A, Baselga E, Drolet BA, et al. Juvenile xanthogranuloma. *J Am Acad Dermatol* 1997;36:355–67.
- Zvulunov A, Barak Y, Metzker A. Juvenile xanthogranuloma, neurofibromatosis, and juvenile chronic myelogenous leukemia. *Arch Dermatol* 1995;131:904–8.
- Gruber R, Vassilaki I, Zelger B. Concomitant juvenile xanthogranuloma and cutaneous mastocytosis in a 3-year-old Swedish girl: case report and review of the literature. *Int J Dermatol* 2011;50:611–14.
- Bains A, Parham DM. Langerhans cell histiocytosis preceding the development of juvenile xanthogranuloma: a case and review of recent developments. *Pediatr Dev Pathol* 2011;14: 480–4.
- Jesenak M, Plamenova I, Plank L, et al. Wiskott-Aldrich syndrome caused by a new mutation associated with multifocal juvenile xanthogranulomas. *Pediatr Dermatol* 2013;30(5): e91–3.
- Aparicio G, Mollet J, Bertralt R, et al. Eruptive juvenile xanthogranuloma associated with relapsing acute lymphoblastic leukemia. *Pediatr Dermatol* 2008;24:487–8.
- Resnick SD, Woosly J, Azizkhan RG. Giant juvenile xanthogranuloma: Exophytic and endophytic variants. *Pediatr Dermatol* 1990;7: 185–8.
- Torrelo A, Juarez A, Hernandez A, et al. Multiple lichenoid juvenile xanthogranuloma. *Pediatr Dermatol* 2009;26:238–40.
- Freyer DR, Kennedy R, Bostrom BC, et al. Juvenile xanthogranuloma: Forms of systemic disease and their clinical implications. *J Pediatr* 1996;129:227–37.
- Chang MW, Frieden IJ, Good W. The risk of intraocular juvenile xanthogranuloma: Survey of current practices and assessment of risk. *J Am Acad Dermatol* 1996;34:445–9.
- Weitzman S, Jaffe R. Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. *Pediatr Blood Cancer* 2005;45:256–64.
- Tan K-W, Koh MJA, Tay Y-K. Juvenile xanthogranuloma in monozygotic twins. *Pediatr Dermatol* 2010;27:666–7.
- Chantorn R, Wisuthsarewong W, Aanpreung P, et al. Severe congenital systemic juvenile xanthogranuloma in monozygotic twins. *Pediatr Dermatol* 2008;25:470–3.
- Newman CC, Raimer SS, Sanchez RL. Nonlipidized juvenile xanthogranuloma: A histologic and immunohistochemical study. *Pediatr Dermatol* 1997;14:98–102.

60. Blouin P, Yvert M, Arbion F, et al. Juvenile xanthogranuloma with hematological dysfunction treated with 2CDA-AraC. *Pediatr Blood Cancer* 2010;55:757–60.
61. Zelger BW, Cerio R. Xanthogranuloma is the archetype of non-Langerhans cell histiocytosis. *Br J Dermatol* 2001;145:369–70.
62. Sidwell RU, Francis N, Slater DN, et al. Is disseminated juvenile xanthogranulomatosis benign cephalic histiocytosis? *Pediatr Dermatol* 2005;22:40–3.
63. Weston WL, Travers SH, Mierau GW, et al. Benign cephalic histiocytosis with diabetes insipidus. *Pediatr Dermatol* 2000;17:296–8.
64. D'Auria AA, De Clerck B, Kim G. Benign cephalic histiocytosis with S-100 positivity. *J Cutan Pathol* 2011;38:842–3.
65. Sell EJ, Hansen RC, Struck-Pierce S. Calcified nodules of the heel: A complication of neonatal intensive care. *J Pediatr* 1985;96:473–5.
66. Leung A. Calcification following heel sticks. *J Pediatr* 1985;106:168.
67. Fretzin DF, Arias AM. Sclerema neonatorum and subcutaneous fat necrosis of the newborn. *Pediatr Dermatol* 1987;4:112–22.
68. Glover MT, Catterall MD, Atherton DJ. Subcutaneous fat necrosis in two infants after hypothermic cardiac surgery. *Pediatr Dermatol* 1991;8:210–12.
69. Chuang SD, Chiu HC, Chang CC. Subcutaneous fat necrosis of the newborn complicating hypothermic cardiac surgery. *Br J Dermatol* 1995;132:805–10.
70. Duhn R, Schoen E, Sui M. Subcutaneous fat necrosis with extensive calcification after hypothermia in two newborn infants. *Pediatrics* 1968;41:661–4.
71. Beers BB, Flowers FP, Sherertz EF, et al. Dystrophic calcinosis cutis secondary to intrauterine herpes simplex. *Pediatr Dermatol* 1986;3:208–11.
72. Ruiz-Maldonado R, Duran-McKinster C, Carrasco-Daza D, et al. Intrauterine epidermal necrosis: report of three cases. *J Am Acad Dermatol* 1998;38:712–15.
73. Carruthers J, Jevon G, Prendiville J. Localized dystrophic periocular calcification: A complication of intralesional corticosteroid therapy for infantile periocular hemangiomas. *Pediatr Dermatol* 1998;15:23–6.
74. Walsh JS, Fairley JA. Calcifying disorders of the skin. *J Am Acad Dermatol* 1995;33:693–706.
75. Zouboulis CC, Blume-Peytavi U, Lennert T, et al. Fulminant metastatic calcinosis with cutaneous necrosis in a child with end-stage renal disease and tertiary hyperparathyroidism. *Br J Dermatol* 1996;135:617–22.
76. Plott T, Wiss K, Raimer SS, et al. Recurrent subepidermal calcified nodule of the nose. *Pediatr Dermatol* 1988;5:107–11.
77. Evans MJ, Blessing K, Gray ES. Subepidermal calcified nodule in children: A clinicopathologic study of 21 cases. *Pediatr Dermatol* 1995;12:307–10.
78. Lai CH, Farah R, Mallory SB. Congenital calcinosis cutis of the ear. *J Am Acad Dermatol* 2003;49:122–4.
79. Bostrum B. Tumoral calcinosis in an infant. *Am J Dis Child* 1981;135:246–7.
80. Heydemann JS, McCarthy RE. Tumoral calcinosis in a child. *J Pediatr Orthop* 1988;8:474–7.
81. Greenberg SB. Tumoral calcinosis in an infant. *Pediatr Radiol* 1990;20:206–7.
82. Niall DM, Fogarty EE, Dowling FE, et al. Spontaneous regression of tumoral calcinosis in an infant: A case report. *J Pediatr Surg* 1998;33:1429–31.
83. Polykandriotis EP, Beutel FK, Horch RE, et al. A case of familial tumoral calcinosis in a neonate and review of the literature. *Arch Orthop Traum Surg* 2004;124:563–7.
84. Sprecher E. Familial tumoral calcinosis: from characterization of a rare phenotype to the pathogenesis of ectopic calcification. *J Invest Dermatol* 2010;130:652–60.
85. Sahn EE, Smith DJ. Annular dystrophic calcinosis cutis in an infant. *J Am Acad Dermatol* 1992;6:1015–17.
86. Puig L, Rocamora V, Romani J, et al. Calcinosis cutis following calcium chloride electrode paste application for auditory-brainstem evoked potentials recording. *Pediatr Dermatol* 1998;15:27–30.
87. Mantovani G. Pseudohypoparathyroidism diagnosis and treatment. *J Clin Endocrinol* 2011;96:3020–30.
88. Miller ES, Esterly NB, Fairley JA. Progressive osseous heteroplasia. *Arch Dermatol* 1996;132:787–91.
89. Talsania N, Jolliffe V, O'Toole E, et al. Platelike osteoma cutis. *J Am Acad Dermatol* 2011;64:613–15.
90. Gardner RJM, Yun K, Craw SM. Familial ectopic ossification. *J Med Genet* 1988;25:113–17.
91. Shore EM, Ahn J, de Beur J, et al. Paternally inherited inactivating mutations of the GNAS1 gene in progressive osseous heteroplasia. *N Engl J Med* 2002;246:99–106.
92. Kaplan KS, Craver R, MacEwan GD, et al. Progressive osseous heteroplasia: A distinct developmental disorder of heterotopic ossification. *J Bone Joint Surg* 1994;76A:425–36.
93. Schmidt AH, Vincent KA, Aiona MD. Hemimelic progressive osseous heteroplasia. *J Bone Joint Surg* 1994;76A:907–12.
94. Schimmel RJ, Pasmans SGMA, Xu M, et al. GNAS – associated disorders of cutaneous ossification: two different clinical presentations. *Bone* 2010;46:868–72.
95. Juppner H. The genetic basis of progressive osseous heteroplasia. *N Engl J Med* 2002;346:128–30.
96. Kaplan FS. Skin and bones. *Arch Dermatol* 1996;132:815–18.
97. Lietman SA, Ding C, Cooke DW, et al. Reduction in Gsalpha induces osteogenic differentiation in human mesenchymal stem cells. *Clin Orthop Relat Res* 2005;434:231–8.
98. Moehlenbeck FW. Pilomatricoma (calcifying epithelioma): a statistical study. *Arch Dermatol* 1973;108:532–4.
99. Pirouzmanesh ABS, Reinisch JF, Gonzalez-Gomez I, et al. Pilomatricoma: a review of 346 cases. *Plast Reconstr Surg* 2003;112:1784–9.
100. Demircan M, Balik E. Pilomatricoma in children: a prospective study. *Pediatr Dermatol* 1997;14:430–2.
101. Trufant J, Kurz W, Franke A, et al. Familial multiple pilomatricomas as a presentation of attenuated adenomatous polyposis coli. *J Cutan Pathol* 2012;39:440–3.
102. Julian CG, Bowers PW. A clinical review of 209 pilomatricomas. *J Am Acad Dermatol* 1998;39:191–5.
103. Geh JL, Moss AL. Multiple pilomatricomata and myotonic dystrophy: a familial association. *Br J Dermatol* 1999;52:143–5.
104. Kopeloff I, Orlow SJ, Sanchez MR. Multiple pilomatricomas: report of two cases and review of the association with myotonic dystrophy. *Cutis* 1992;50:290–2.
105. Cambiaghi S, Ermacora E, Brusasco A, et al. Multiple pilomatricomas in Rubinstein-Taybi syndrome: a case report. *Pediatr Dermatol* 1994;11:21–5.
106. Chan EF, Gat U, McNiff JM, et al. A common skin tumour is caused by activating mutations in beta-catenin. *Nature Genet* 1999;21:410–13.
107. Hughes J, Lam A, Rogers M. Use of ultrasonography in the diagnosis of childhood pilomatricoma. *Pediatr Dermatol* 1999;16:341–4.
108. Prendiville JS. Granuloma annulare. In: Goldsmith LA, Katz SI, Gilchrist BA, et al, editors. *Fitzpatrick's dermatology in general medicine*. 8th ed. New York: McGraw Hill; 2012. p. 467–72.
109. Lee SW, Cheong SH, Byun JY, et al. Generalized granuloma annulare in infancy following *Bacillus Calmette-Guerin* vaccination. *Ann Dermatol* 2011;23:S319–21.
110. Choi J-C, Bae J-Y, Cho S, et al. Generalized perforating granuloma annulare in an infant. *Pediatr Dermatol* 2003;20:131–3.
111. Hata N, Inamura T, Imayama S, et al. Multiple palisading granulomas in the scalp of an infant; a case report. *Surg Neurol* 2001;56:396–9.
112. De Aloe G, Risulo M, Sbrano P, et al. Congenital subcutaneous granuloma annulare. *Pediatr Dermatol* 2005;22:234–236.
113. Wagner G, Schmoll J, Sachse MM. Linear granuloma annulare in an infant – an unusual clinical presentation. *J Dtsch Dermatol Ges* 2012;10:434–5.
114. Poomechaiwong S, Golitz LE. Hamartomas. *Adv Dermatol* 1990;5:257–88.
115. Happle R. The group of epidermal nevus syndromes: Part I. Well-defined phenotypes. *J Am Acad Dermatol* 2010;63:1–22.
116. Nazarro V, Ermacora E, Santucci B, et al. Epidermolytic hyperkeratosis: Generalized form in children from parents with systematized linear form. *Br J Dermatol* 1990;122:417–22.
117. Happle R, Rogers M. Epidermal nevi. *Adv Dermatol* 2002;18:175–201.
118. Happle R. The group of epidermal nevus syndromes: Part II. Less well defined phenotypes. *J Am Acad Dermatol* 2010;63:25–30.
119. Levisohn JL, Tian LC, Boyden LM, et al. Whole genome sequencing reveals somatic mutations in HRAS and KRAS, which cause nevus sebaceus. *J Invest Dermatol* 2013;133(3):827–30.
120. Vidaurri-de la Cruz H, Tamayo-Sanchez L, Duran-McKinster C, et al. Epidermal nevus syndromes: clinical findings in 35 patients. *Pediatr Dermatol* 2004;4:432–9.
121. Davies D, Rogers M. Review of neurological manifestations in 196 patients with sebaceous naevi. *Australas J Dermatol* 2002;43:20–3.
122. Palazzi P, Artese O, Paolini A, et al. Linear sebaceous nevus syndrome: Report of a patient with unusual associated abnormalities. *Pediatr Dermatol* 1996;13:22–4.
123. Goldblum JR, Headington JT. Hypophosphatemic vitamin D-resistant rickets and multiple spindle and epithelioid nevi associated with linear nevus sebaceus syndrome. *J Am Acad Dermatol* 1993;29:109–11.
124. Oranje AP, Przyrembel H, Meradji M, et al. Solomon's epidermal nevus syndrome (Type: linear sebaceous nevus) and hypophosphatemic

- vitamin D-resistant rickets. *Arch Dermatol* 1994;130:1167-71.
125. Greene AK, Rogers GF, Mulliken JB. Schimmelpenning syndrome: an association with vascular anomalies. *Cleft Palate Craniofac J* 2007;44:208-15.
 126. Lam J, Dohil MA, et al. SCALP syndrome: sebaceous nevus syndrome, CNS malformations, aplasia cutis congenita, limbal dermoid, and pigmented nevus (giant congenital melanocytic nevus) with neurocutaneous melanosis: a distinct syndromic entity. *J Am Acad Dermatol* 2008;58:884-8.
 127. Groesser L, Hershberger E, Ruetten A, et al. Postzygotic HRAS and KRAS mutations cause nevus sebaceous and Schimmelpenning syndrome. *Nat Genet* 2012;44:783-7.
 128. Benedetto L, Sood U, Blumenthal N, et al. Familial nevus sebaceous. *J Am Acad Dermatol* 1990;23:130-2.
 129. Sahl WJ. Familial nevus sebaceous of Jadassohn: occurrence in three generations. *J Am Acad Dermatol* 1990;22:853-4.
 130. Happle R. How many epidermal nevus syndromes exist? A clinicogenetic classification. *J Am Acad Dermatol* 1991;25:550-6.
 131. Drolet BA, Prendiville J, Golden J, et al. Membranous aplasia cutis with hair collars: Congenital absence of the skin or neuroectodermal defect. *Arch Dermatol* 1997;133:1551-4.
 132. Heilig S, Koslosky K, Ioffreda MD, et al. Eczematous nevus sebaceous: a report of three cases. *Pediatr Dermatol* 2011;28:176-9.
 133. Domingo J, Helwig EB. Malignant neoplasms associated with nevus sebaceous of Jadassohn. *J Am Acad Dermatol* 1979;1:545-56.
 134. Cribier B, Scrivener Y, Grosshans E. Tumors arising in nevus sebaceous: a study of 596 cases. *J Am Acad Dermatol* 2000;42:263-8.
 135. Jaqueti G, Requena L, Sanchez Yus E. Trichoblastoma is the most common neoplasm developed in nevus sebaceous of Jadassohn: a clinicopathologic study of a series of 155 cases. *Am J Dermatopathol* 2000;22:108-18.
 136. Santibanez-Gallerani A, Marshall D, Duarte A-M, et al. Should nevus sebaceous of Jadassohn in children be excised? A study of 757 cases, and literature review. *J Craniofac Surg* 2003;14:658-60.
 137. Ghosh SK, Bandyopadhyay D, Chatterjee G, et al. Syringocystadenoma papilliferum: an unusual presentation. *Pediatr Dermatol* 2009;26:758-9.
 138. Karg E, Korom I, Varga E, et al. Congenital syringocystadenoma papilliferum. *Pediatr Dermatol* 2008;25:132-3.
 139. Patterson JW, Straka BF, Wick MR. Linear syringocystadenoma papilliferum of the thigh. *J Am Acad Dermatol* 2001;45:139-41.
 140. Schaffer JV, Cantatore-Francis JL, Shin HT, et al. Syringocystadenoma papilliferum in a patient with focal dermal hypoplasia due to a novel PORCN mutation. *Arch Dermatol* 2009;145:218-19.
 141. Jordan JA, Brown OE, et al. Congenital syringocystadenoma papilliferum of the ear and neck treated with the CO2 laser. *Int J Pediatr Otorhinolaryngol* 1996;38:81-7.
 142. Zhang YH, Wang W-L, Rapini RP, et al. Syringocystadenocarcinoma papilliferum with transition to areas of squamous differentiation: a case report and review of the literature. *Am J Dermatopathol* 2012;34:428-33.
 143. Tay Y-K, Weston WL, Ganong CA, et al. Epidermal nevus syndrome: association with central precocious puberty and woolly hair nevus. *J Am Acad Dermatol* 1996;35:839-42.
 144. Torrelo A, Colmenero I, Kristal L, et al. Papular epidermal nevus with 'skyline' basal cell layer (PENS). *J Am Acad Dermatol* 2011;64:888-92.
 145. Elam CA, McCleskey MP. White epidermal nevi at birth in a patient with tuberous sclerosis. *Pediatr Dermatol* 2012; Oct 9, doi: 10.1111/pde.12005 [Epub ahead of print].
 146. Rodriguez-Diaz E, Gonzalo P, Colmenero I, et al. Papular epidermal nevus with 'skyline' basal cell layer (PENS) with extracutaneous findings. *Pediatr Dermatol* 2013;30(4):e54-6.
 147. Tadini G, Restano L, Happle R, et al. PENS syndrome: a new neurocutaneous phenotype. *Dermatology* 2012;224:24-30.
 148. Munro CS, Cox NH. An acantholytic dyskeratotic epidermal naevus with other features of Darier's disease on the same side of the body. *Br J Dermatol* 1992;127:168-71.
 149. Stosiek N, Ulmer R, von den Driesch P, et al. Chromosomal mosaicism in two patients with epidermal verrucous nevus: demonstration of chromosomal breakpoint. *J Am Acad Dermatol* 1994;30:622-5.
 150. Iglesias Zamora ME, Vazquez-Doval FJ. Epidermal naevi associated with trichilemmal cysts and chromosomal mosaicism. *Br J Dermatol* 1997;137:821-4.
 151. Tsubota A, Akiyama M, Sakai K, et al. Keratin 1 gene mutation detected in epidermal nevus with epidermolytic hyperkeratosis. *J Invest Dermatol* 2007;127:1371-4.
 152. Nelson BR, Kolansky G, Gillard M, et al. Management of linear verrucous epidermal nevus with topical 5-fluorouracil and tretinoin. *J Am Acad Dermatol* 1994;30:287.
 153. Cestari T, Rubim M, Valentini BC. Nevus comedonicus: case report and brief review of the literature. *Pediatr Dermatol* 1991;8:300-5.
 154. Patrizi A, Neri I, Fiorentini C, et al. Nevus comedonicus syndrome: a new pediatric case. *Pediatr Dermatol* 1998;15:304-6.
 155. Kim SC, Kang WH. Nevus comedonicus associated with epidermal nevus. *J Am Acad Dermatol* 1989;21:1085-8.
 156. Vassiloudes PE, Morelli JP, Weston WL. Inflammatory nevus comedonicus in children. *J Am Acad Dermatol* 1998;38:834-6.
 157. Munro CS, Wilkie AO. Epidermal mosaicism producing localized acne: somatic mutation in FGFR2. *Lancet* 1998;352:704-5.
 158. Itin PH, Happle R. Tinschert syndrome: segmentally arranged basaloid follicular hamartomas, linear atrophoderma with hypo- and hyperpigmentation, enamel defects, ipsilateral hypertrichosis, and skeletal and cerebral anomalies. *Dermatology* 2009;218:221-5.
 159. Marcus J, Esterly NB, Bauer BS. Tissue expansion in a patient with extensive nevus comedonicus. *Ann Plast Surg* 1992;29:362-6.
 160. Goddard DS, Rogers M, Frieden IJ, et al. Widespread porokeratotic adnexal ostial nevus: clinical features and proposal of a new name unifying porokeratotic eccrine ostial and dermal duct nevus and porokeratotic eccrine and hair follicle nevus. *J Am Acad Dermatol* 2009;61(6):1060, e1-14.
 161. Abell E, Read SI. Porokeratotic eccrine ostial and dermal duct naevus. *Br J Dermatol* 1980;103:435-41.
 162. Leung CS, Tang WY, Lam WY, et al. Porokeratotic eccrine ostial and dermal duct naevus. *Br J Dermatol* 1998;138:684-8.
 163. Aloï F, Pippione M. Porokeratotic eccrine ostial and dermal duct nevus. *Arch Dermatol* 1986;122:892-5.
 164. Jamora MJ, Celis MA. Generalized porokeratotic eccrine ostial and dermal duct nevus associated with deafness. *J Am Acad Dermatol* 2008;59(2 Suppl 1):S43-5.
 165. Lazic T, Li Q, Frank M, et al. Extending the phenotypic spectrum of keratitis-ichthyosis-deafness syndrome: report of a patient with GJB2 (G12R) connexin 26 mutation and unusual clinical findings. *Pediatr Dermatol* 2012;29:349-57.
 166. Easton JA, Donnelly S, Kamps MA, et al. Porokeratotic eccrine nevus may be caused by somatic connexin26 mutations. *J Invest Dermatol* 2012;132:2184-91.
 167. Jain S, Sardana K, Garg VK. Ultrapulse carbon dioxide laser treatment of porokeratotic eccrine ostial and dermal duct nevus. *Pediatr Dermatol* 2013;30(2):264-6.
 168. Zvulunov A, Rotem A, Merlob P, et al. Congenital smooth muscle hamartoma. Prevalence, clinical findings, and follow-up in 15 patients. *Am J Dis Child* 1990;144(7):782-4.
 169. Sato M, Ishiwawa O, Miyachi Y, et al. Michelin tyre syndrome: A congenital disorder of elastic fibre formation. *Br J Dermatol* 1997;136:583-6.
 170. Oku T, Iwasaki K, Fujita H. Folded skin with an underlying cutaneous smooth muscle hamartoma. *Br J Dermatol* 1993;129:606-8.
 171. Schnur RE, Herzberg AJ, Spinner N, et al. Variability in the Michelin tyre syndrome: A child with multiple anomalies, smooth muscle hamartoma, and familial paracentric inversion of chromosome 7q102. *J Am Acad Dermatol* 1993;28:364-70.
 172. Holland KE, Galbraith SS. Generalized congenital smooth muscle hamartoma presenting with hypertrichosis, excess skin folds, and follicular dimpling. *Pediatr Dermatol* 2008;25:236-9.
 173. Johnson MD, Jacobs AH. Congenital smooth muscle hamartoma. *Arch Dermatol* 1989;125:820-2.
 174. Gagne EJ, Su WPD. Congenital smooth muscle hamartoma of the skin. *Pediatr Dermatol* 1993;10:142-5.
 175. Grau-Massanes M, Raimer S, Colome-Grimmer M, et al. Congenital smooth muscle hamartoma presenting as a linear atrophic plaque: Case report and review of the literature. *Pediatr Dermatol* 1996;13:222-5.
 176. Guillot B, Huet P, Joujoux JM, et al. Multiple congenital smooth muscle hamartomas. *Ann Dermatol Venerol* 1998;125:118-20.
 177. Happle R, Koopman RJ. Becker nevus syndrome. *Am J Med Genet* 1997;68:357-61.
 178. Book SE, Glass AT, Laude TA. Congenital Becker's nevus with a familial association. *Pediatr Dermatol* 1997;14:373-5.
 179. Lambert JR, Willems P, Abs R, et al. Becker's nevus associated with chromosomal mosaicism and congenital adrenal hyperplasia. *J Am Acad Dermatol* 1994;30:655-7.
 180. Ferreira MJ, Bajanca R, Fiadeiro T. Congenital melanosis and hypertrichosis in a bilateral distribution. *Pediatr Dermatol* 1998;15:290-2.
 181. Urbani CE, Betti R. Supernumerary nipple in association with Becker nevus vs. Becker nevus

- syndrome: A semantic problem only. *Am J Med Genet* 1998;77:76–7.
182. Happle R. Patterns on the skin. New aspects of their embryologic and genetic causes. *Hautarzt* 2004;55:960–8.
 183. Nomura Y, Ota M, Tochimaru H. Self-healing congenital generalized skin creases: Michelin tire baby syndrome. *J Am Acad Dermatol* 2010;63:1110–11.
 184. Kharfi M, Zaraq I, Chaouechi M, et al. Michelin tire syndrome: a report of two siblings. *Pediatr Dermatol* 2005;22:245–9.
 185. Wouters L, Rodriguez Rodriguez CM, Porta Dapena E, et al. Circumferential skin creases, cleft palate, typical face, intellectual disability and growth delay: ‘circumferential skin creases Kunze type’. *Eur J Med Genet* 2011; 54:236–40.
 186. Lane JE, Clark E, Marzec T. Nevus lipomatosus cutaneous superficialis. *Pediatr Dermatol* 2003;20:313–14.
 187. Happle R, Küster W. Nevus psiloliparus: a distinct fatty tissue nevus. *Dermatology* 1998; 197:6–10.
 188. Uitto J, Santa Cruz DJ, Eisen AZ. Connective tissue nevi of the skin: Clinical, genetic and histopathologic classification of hamartomas of the collagen, elastin and proteoglycan type. *J Am Acad Dermatol* 1980; 3:441–61.
 189. Saussine A, Marrou K, Delanoe P, et al. Connective tissue nevi: an entity revisited. *J Am Acad Dermatol* 2012;67:233–9.
 190. Verbov J, Graham R. Buschke–Ollendorff syndrome-disseminated dermatofibrosis with osteopoikilosis. *Clin Exp Dermatol* 1986;11: 17–26.
 191. Botella-Estrada R, Alegre V, Sanmartin O, et al. Isolated plantar cerebriform collagenoma. *Arch Dermatol* 1991;127:1589–90.
 192. Chang S-E, Kang S-K, Kim E-S, et al. A case of congenital mucinous nevus: a connective tissue nevus of the proteoglycan type. *Pediatr Dermatol* 2003;20:229–31.
 193. Clarke JT, Clarke LE, Miller C, et al. Plaque-like myofibroblastic tumor of infancy. *Pediatr Dermatol* 2007;24:E83–7.
 194. Marqueling AL, Dasher D, Friedlander SF, et al. Plaque-like myofibroblastic tumor: report of three cases. *Pediatr Dermatol* 2013;30(5): 600–7.
 195. de Feraudy S, Fletcher C. Fibroblastic connective tissue nevus. *Am J Surg Pathol* 2012;36: 1509–15.
 196. Meggitt SJ, Harper J, Lacour M, et al. Raised limb bands developing in infancy. *Br J Dermatol* 2002;147:359–63.
 197. Dyer JA, Chamlin S. Acquired raised bands of infancy: association with amniotic bands. *Pediatr Dermatol* 2005;22:346–9.
 198. Lateo SA, Taylor AEM, Meggitt SJ. Raised limb bands developing in infancy. *Br J Dermatol* 2006;154:791–2.

KEY REFERENCES

1. Coffin CM, Alaggio R. Fibromyoblastic and myofibroblastic tumors in children and adolescents. *Pediatr Dev Pathol* 2012;15(Suppl. 1):127–80.
56. Weitzman S, Jaffe R. Uncommon histiocytic disorders: the non-Langerhans cell histiocytoses. *Pediatr Blood Cancer* 2005;45:256–64.
84. Sprecher E. Familial tumoral calcinosis: from characterization of a rare phenotype to the pathogenesis of ectopic calcification. *J Invest Dermatol* 2010;130:652–60.
87. Mantovani G. Pseudohypoparathyroidism diagnosis and treatment. *J Clin Endocrinol* 2011;96:3020–30.
115. Happle R. The group of epidermal nevus syndromes: Part I. Well-defined phenotypes. *J Am Acad Dermatol* 2010;63:1–22.
118. Happle R. The group of epidermal nevus syndromes: Part II. Less well defined phenotypes. *J Am Acad Dermatol* 2010;63:25–30.
127. Groesser L, Hershberger E, Ruetten A, et al. Postzygotic HRAS and KRAS mutations cause nevus sebaceous and Schimmelpenning syndrome. *Nat Genet* 2012;44:783–7.
160. Goddard DS, Rogers M, Frieden IJ, et al. Widespread porokeratotic adnexal ostial nevus: clinical features and proposal of a new name unifying porokeratotic eccrine and dermal duct nevus and porokeratotic eccrine and hair follicle nevus. *J Am Acad Dermatol* 2009;61(6):1060, e1–14.
166. Easton JA, Donnelly S, Kamps MA, et al. Porokeratotic eccrine nevus may be caused by somatic connexin26 mutations. *J Invest Dermatol* 2012;132:2184–91.
189. Saussine A, Marrou K, Delanoe P, et al. Connective tissue nevi: an entity revisited. *J Am Acad Dermatol* 2012;67:233–9.

Disorders of the Subcutaneous Tissue

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Introduction

The subcutaneous fat cushions the overlying skin, insulates and provides energy storage, and protects underlying soft tissue and bony structures. Although not fully functional at birth, a well-developed fatty layer is present in the neonate, even when premature.¹ Disorders of the fat can interfere with normal function and may have systemic implications.

The nomenclature and classification of subcutaneous fat disorders of the newborn are inconsistent and confusing. However, a number of entities have been recognized because of their distinctive clinical patterns, histopathology, biochemical and genetic markers, inheritance, and course. The clinician must distinguish disorders that are innocent and self-limiting from those that are associated with significant morbidity or underlying systemic disease.

Subcutaneous fat necrosis of the newborn

Subcutaneous fat necrosis of the newborn (SCFN) is an uncommon disorder that occurs primarily in full-term and post-mature infants during the first few weeks of life. Although lesions can develop in infants with a normal delivery and neonatal course, SCFN has been associated with perinatal complications, including asphyxia, hypothermia, seizures, pre-eclampsia, meconium aspiration, and intrapartum medication.²⁻⁵ Extensive subcutaneous fat necrosis has also been reported following therapeutic hypothermia used in newborns with severe perinatal asphyxia and surgical procedures.⁶⁻⁸

Although the first reports of SCFN appeared during the early nineteenth century, many investigators continued to use the terms scleroderma or scleredema to describe SCFN, as well as a number of diverse disorders of the subcutaneous tissue associated with the development of distinct nodules or widespread induration. Over a century later, the term subcutaneous fat necrosis was first applied to this clinically benign condition with histologic characteristics of fat necrosis.⁵

Cutaneous findings

Affected infants typically present with one or several indurated, variably circumscribed, violaceous or red plaques or subcutaneous nodules from one to several centimeters in diameter on the buttocks, thighs, trunk, face, and/or arms (Figs 27.1–27.4). In some cases, the nodules may be subtle, not associated with overlying color change, and only appreciated by careful palpation of the underlying fat. Rarely, large plaques may cover extensive areas of the trunk or extremities. However, lesions are usually freely movable over subjacent muscles and fascia. Although SCFN may be tender, affected infants are afebrile and usually asymptomatic.

Most SCFN regresses spontaneously without scarring over several weeks to months. Rarely nodules persist for over 6 months.⁹ Occasionally, fluctuance and abscess-like changes occur, resulting in spontaneous drainage and scar formation. Variable amounts of calcification develop, which can be appreciated radiographically.¹⁰

Etiology and pathogenesis

Some investigators have proposed that SCFN results from hypoxic injury to fat caused by local trauma, particularly in the child with perinatal complications.^{11,12} This is supported by the observation that fat necrosis occurs commonly over bony prominences. Others have suggested that the susceptibility to SCFN results from an increased proportion of the saturated fats palmitic and stearic acid, relative to the monounsaturated fat oleic acid in neonatal subcutaneous tissue.^{9,11,13} Saturated fatty acids have a higher melting point than unsaturated fats, which may predispose newborn fat to crystallization at higher ambient temperatures than fat in older children and adults. Consequently, even in the setting of mild hypothermia, crystallization of fat may occur, with subsequent fat necrosis. Finally, an underlying defect in neonatal fat composition or metabolism, possibly related to immaturity, in the setting of perinatal stress, may lead to fat necrosis.

Diagnosis

Although SCFN is usually diagnosed clinically, when the presentation is atypical or the infant is ill, the diagnosis can be confirmed by skin biopsy showing the characteristic histopathologic findings of patchy areas of necrosis and crystallization of fat. The involved fat lobules contain pathognomonic needle-shaped clefts surrounded by a mixed inflammatory infiltrate composed of lymphocytes, histiocytes, fibroblasts, and foreign body giant cells.⁵ Fine-needle aspiration biopsy is a safe and reliable alternative.¹⁴

Although laboratory tests are usually normal, hypercalcemia occurs occasionally from 1 to 4 months after the appearance of skin lesions.^{9,11-13} The risk of hypercalcemia increases with the severity of the perinatal insult and extent of fat necrosis.¹⁵ Rarely hypercalcemia is severe, and has been implicated in the deaths of three infants. Nephrocalcinosis, vomiting, failure to thrive, poor weight gain, irritability, and seizures can complicate high calcium levels or chronic moderate elevations.^{2,7} Although the exact cause of hypercalcemia is unknown, several explanations, including elevated parathyroid hormone levels, prostaglandin E₂ release, calcium release from necrotic fat, and elevated levels of vitamin D, have been proposed. Calcitriol produced by macrophages in the inflammatory infiltrate of SCFN with increased calcium absorption in the gastrointestinal tract is the favored explanation.^{4,5,11-13}



Figure 27.1 Fat necrosis of the temple secondary to forceps injury.



Figure 27.2 Extensive fat necrosis involving the back, upper arm, and thigh. This infant also had transient thrombocytopenia.



Figure 27.3 This 8-day-old boy with a history of perinatal asphyxia and seizures developed subcutaneous fat necrosis on the second day of life, with widespread nodules and plaques on the back, abdomen, and proximal extremities.



Figure 27.4 This healthy vigorous newborn developed violaceous nodules on his left elbow and right posterior upper arm at 5 days of age.

Soft tissue calcification may occur in the absence of hypercalcemia and can be detected radiographically. Tests of parathyroid function, vitamin D metabolites, and urinary prostaglandins may be useful in the evaluation of infants with hypercalcemia. Hypocalcemia with pseudohypoparathyroidism requiring therapy,¹⁶ as well as transient hypoglycemia, hypertriglyceridemia, and thrombocytopenia,¹⁷ have also been reported in several children.

Differential diagnosis

The subcutaneous nodules that follow the abrupt withdrawal of systemic steroids can be difficult to distinguish from those of SCFN. However, they usually occur on the cheeks, arms, and trunk 1–2 weeks after discontinuation of steroids. SCFN can be distinguished from sclerema neonatorum, lipogranulomatosis, infectious panniculitis, and nodular panniculitis by the general well-being of the infant with SCFN and characteristic clinical and histopathologic features. Infants with sclerema neonatorum present with diffuse skin stiffness and severe multisystem disease. Deep soft tissue infections in neonates are usually associated with fever and other signs of sepsis. Subcutaneous hemangiomas, soft tissue tumors such as rhabdomyosarcomas, fibromatosis of infancy, and histiocytosis can be excluded by imaging studies, disease course, and histologic findings. When hypercalcemia and/or soft tissue calcification is present, primary hyperparathyroidism, osteoma cutis, and calcification associated with Albright osteodystrophy should be excluded.

Management

In most infants with SCFN, treatment is limited to parental reassurance and supportive measures.^{4,11–13} Hypercalcemia, if present, may have clinical signs such as poor growth or irritability, or may be entirely asymptomatic. Although onset is most commonly noted at 4–6 weeks of age and usually resolves by 4 months, some cases have reported to persist for 6 months. As a consequence, at-risk infants should be monitored for the first 6 months of life and should not receive vitamin D supplementation for rickets prophylaxis during this period.^{3,15} Treatment of hypercalcemia may require intravenous saline, calcium-wasting diuretics, and rarely, intravenous corticosteroids. Etidronate therapy has also been reported to be successful in controlling severe hypercalcemia in SCFN.¹³ Ulcerated lesions, which rarely

occur in otherwise healthy infants, usually respond to topical antibiotics and bio-occlusive dressings.

Sclerema neonatorum

Sclerema neonatorum is a rare clinical finding rather than a distinct disorder that affects debilitated term and premature infants during the first 1–2 weeks of life.⁵ It occasionally occurs in older infants up to 4 months of age with severe underlying disease. Over the last decade, it has only rarely been reported in North America, but the persistence of cases in the developing world is probably related to an increased risk of malnutrition, diarrheal disease, low birthweight and subsequent sepsis.^{18,19}

Cutaneous findings

Diffuse hardening of the skin usually appears suddenly on the 3rd or 4th day of life, starting over the lower extremities, especially the calves, spreading to the thighs, buttocks, and cheeks, and eventually the trunk.^{5,20–24} Sclerema eventually involves most of the skin, particularly in premature infants, with the exception of the palms, soles, and genitals. The skin feels cold, smooth, hard, and bound down. The joints are immobile, and the face appears mask-like.

Extracutaneous findings

Affected infants are usually poorly nourished, dehydrated, hypotensive, hypothermic, and septic. Necrotizing enterocolitis, pneumonia, intracranial hemorrhage, hypoglycemia, and electrolyte disturbances are also often associated with sclerema.^{5,21–26}

In most cases, sclerema is limited to the subcutaneous fat. However, in two infants, autopsy revealed identical changes in the visceral fat.²⁷

Etiology and pathogenesis

The development of sclerema is probably a result of dysfunction of the neonatal enzymatic system involved in the conversion of saturated palmitic and stearic acids to unsaturated oleic acid. Immaturity of the neonatal lipoenzymes is further compromised by hypothermia, infection, shock, dehydration, and surgical and environmental stresses. The relative abundance of saturated fatty acids and depletion of unsaturated fatty acid allows for fat solidification to occur more readily, with the subsequent development of sclerema.^{5,20,21}

Diagnosis

On gross pathologic examination, the subcutaneous tissue of affected infants is markedly thickened, firm, and lard-like, with fibrous bands seen to extend from the fat into the lower dermis. Microscopically, early lesions demonstrate distinctive lipid crystals within fat cells, forming rosettes of fine, needle-like clefts.^{5,21} Although there is usually no inflammatory reaction to fat necrosis, occasionally some giant cells are present. Older lesions often show thickened septa, and rarely calcification.

Other laboratory findings in neonates with sclerema are nonspecific and usually reflect the underlying systemic medical problems. Thrombocytopenia, neutropenia, active bleeding, and worsening acidosis carry a poor prognosis.^{5,25,26}

Differential diagnosis

In healthy infants who develop widespread slowly progressive scleroderma-like plaques on the trunk and proximal extremities, the diagnosis of stiff skin syndrome should be considered

(see below). However, this is a primary disorder of fascia and, unlike sclerema, is not associated with systemic symptoms. The lack of inflammation and extensive involvement of the subcutis help to distinguish sclerema from SCFN and cold panniculitis, in which the lesions are localized and associated with exuberant granulomatous inflammation. Diffuse edema resulting from hemolytic anemia, renal, and/or cardiac dysfunction manifests as pitting edema, unlike sclerema. Congenital lymphedema or Milroy disease is nonpitting and often widespread. However, in lymphedema, the infant is otherwise healthy, and a skin biopsy reveals normal fat and dilated lymphatics. Erysipelas or lymphangitis is red, tender, and more localized than sclerema. Diffuse sclerodermatous changes associated with systemic sclerosis, which is extremely rare in the newborn, can also mimic sclerema. However, histology demonstrates characteristic hypertrophy and sclerosis of collagen, which eventually replaces the fat in scleroderma.

Treatment

Attention to the maintenance of a neutral thermal environment, electrolyte and water balance, adequate hydration and ventilation, and aggressive treatment of shock and infection in the modern nursery intensive care unit, undoubtedly account for the extremely low incidence of sclerema today. Although most infants with sclerema succumb to sepsis and shock, reversal of the underlying systemic disease can result in recovery.

The role of systemic steroids in the management of infants with sclerema is controversial. Several investigators have reported a favorable outcome when exchange transfusion was combined with conventional therapy.^{21,26}

Stiff skin syndrome

In 1971, Esterly and McKusick²⁸ described a disorder in infants and young children characterized by diffuse skin induration and thickening, with limitation of joint mobility, flexion contractures, and hypertrichosis. This condition, which has been called ‘congenital fascial dystrophy’ or the ‘stiff skin syndrome’ was further defined by Jablonska and colleagues²⁹ as a generalized, noninflammatory disease of fascia without evidence of visceral or muscle involvement, immunologic abnormalities, or vascular hyperreactivity. Although most cases have been sporadic, disease affecting two siblings,³⁰ a mother and two siblings,²⁸ and another family with affected family members in multiple generations, support a hereditary transmission.³¹

Cutaneous findings

Stiff skin syndrome presents in infancy or early childhood with scleroderma-like plaques initially affecting the trunk and proximal extremities, particularly the buttocks and thighs. In the first stages, the condition may seem subtle and somewhat localized. Progression of the rock-hard indurated bound-down skin over large areas of the body, including the extremities, results in contractures, scoliosis, a narrow thorax, and a characteristic tiptoe gait. A variable increase in hair may be noted over areas of cutaneous involvement.^{28,29,31–35}

Extracutaneous findings

Orthopedic abnormalities result from the cutaneous and fascial plaques that produce contractures, especially over large joints. Although restrictive pulmonary changes and growth retardation have occasionally been reported, immunologic, visceral,

bony, muscular, and vascular involvement is characteristically absent.^{29,32–34}

Etiology and pathogenesis

Although the cause is unclear, investigators have proposed a primary fibroblastic defect resulting in increased mucopolysaccharide deposition in the dermis, a primary fascial dystrophy resulting from increased collagen, and an inflammatory process.^{29,32–34} Some patients with stiff skin syndrome have been noted to have increased myofibroblastic activity in fascia, with overproduction of type VI collagen. Similar findings have been observed in extra-abdominal desmoid tumors, juvenile hyaline fibromatosis, scleroderma, and the tight skin mouse model which is transmitted in an autosomal dominant pattern and is located on chromosome 2.³⁶ Cutaneous fibrosis in the *Tsk* mouse appears to be caused by a mutation in Fibrillin-1. A mutation in Fibrillin-1 has also been demonstrated in 4 families with autosomal dominant stiff skin syndrome.³¹

Diagnosis

In infants and young children with progressive bound-down plaques beginning on the trunk, limited joint mobility, and no evidence of systemic disease, stiff skin syndrome should be considered. Varying histologic changes from patient to patient and in the same patient over time, may reflect different triggers which result in similar clinical findings.^{32–34,36} In some cases, thickening of the collagen in the fascia was noted, whereas in others the fascia was normal and increased mucopolysaccharide deposition was found in the dermis. Noninflammatory sclerosis in the deep reticular dermis extending into the subcutaneous fat has also been noted. A recent report suggests that, although noninflammatory fibrosis of the fat and fascia is typical but not specific for incisional biopsies of stiff skin syndrome, the presence of a lattice-like array of thickened, horizontally oriented collagen bundles may be a clue to diagnosis.³⁷

Differential diagnosis

Firm, woody induration of the skin with joint contractures may occur in geleophysic dysplasia, progeria, neonatal mucopolipidosis II, and Farber lipomatosis. These disorders can be distinguished from stiff skin syndrome by their characteristic clinical, histologic, biochemical, and genetic findings. The clinical features of scleroderma overlap with some cases of stiff skin syndrome. Although thickening of the fascia does not usually occur in scleroderma, in some cases of linear scleroderma, deep soft tissues and bone can be involved. However, the lesions are usually self-limited. Eosinophilic fasciitis, which presents with acral scleroderma-like changes, can also be distinguished by characteristic clinical features, course, and histology. Sclerema neonatorum and subcutaneous fat necrosis of the newborn demonstrate a distinctive panniculitis and clinical course, and infantile systemic hyalinosis can be distinguished by the presence of hyaline deposits in the skin, multiorgan failure, and death in early childhood. In milder cases, the condition may mimic a connective tissue nevus, smooth muscle hamartoma, or myofibroma.

Treatment

Although the disorder is usually slowly progressive, in some patients lesions have been noted to stabilize or improve. Treatment is generally limited to supportive and rehabilitative care.

Panniculitis caused by physical agents

Although physical agents may contribute to the development of SCFN and sclerema neonatorum, a number of environmental factors can cause direct injury to the fat. Cold, heat, mechanical trauma, and chemical injury can lead to the formation of nodules in the fat. The overlying epidermis is usually unaffected in cold and mechanical trauma, whereas bullae, erosions, and ulcerations from epidermal and dermal necrosis characterize heat and chemical insults.

COLD PANNICULITIS

The development of panniculitis following exposure to sub-freezing temperatures was first noted over 70 years ago, by Haxthausen who described four young children and an adolescent with facial plaques.^{38,39} In his paper, he referred to several earlier reports of hardening of the fat associated with cold exposure and the application of ice directly to the skin.^{40,41} Similar cases have been reported following the use of ice to induce hypothermia before cardiac surgery,⁴⁰ and the application of ice bags to the face for management of supraventricular tachycardia.^{41,42} Popsicle panniculitis is a term coined by Epstein in 1970 to refer to a specific subset of cold panniculitis triggered by infants sucking on flavored ice.⁴³ Although lesions may develop in older children and adults, most cases occur in infants under 1 year.

Cutaneous findings

Symmetric, tender, indurated nodules and plaques 1–3 cm in diameter typically appear on the cheeks of infants 1–2 days after cold exposure.^{38,39,42–44} The overlying skin appears red to violaceous (Fig. 27.5), and the infant is otherwise well. In a study by Rotman³⁹ the application of an icecube to the volar aspect of the forearm of an 8-month-old girl resulted in mild transient erythema for 15 min. A red plaque developed 12–18 h later and resolved after 13 days. Lesions usually soften, flatten, and heal over 2–3 weeks, leaving post-inflammatory pigmentary changes, particularly in darkly pigmented individuals.

Etiology and pathogenesis

As in subcutaneous fat necrosis of the newborn and sclerema neonatorum, exposure to low ambient temperatures is thought



Figure 27.5 Erythematous nodule of panniculitis resulting from cold exposure (popsicle).

to result in crystallization of the subcutaneous tissue in infants, which is relatively high in saturated fats compared to that of older children and adults. Applying ice to the skin for 50 seconds results in nodules in all newborns, but only in 40% of 6-month-old and only occasionally in 9-month-old infants.⁴³ In 1966, Duncan and colleagues⁴⁵ described a child in whom nodules followed the application of ice for several minutes at 6 months of age, and 8 min at 18 months of age. When the child was 22 months old, ice applied for 15 min did not trigger panniculitis. The resistance to cold injury correlates with the relative increase in unsaturated fats in the subcutaneous tissue of older infants and children.

Diagnosis

The development of subcutaneous nodules in any neonate or young infant exposed to ice or subfreezing temperatures in the preceding 1–3 days should suggest the diagnosis of cold panniculitis. Histologic changes evolve over several days.⁴⁵ The earliest changes 24 h after cold injury include an infiltrate of macrophages and lymphocytes at the dermoepidermal junction extending into the dermis and fat. At 48 h, the inflammation is more intense and fat necrosis is present. Lipid from ruptured fat cells forms large cystic structures surrounded by histiocytes, neutrophils, and lymphocytes. These changes become more pronounced over the next few days, and subside completely in 2 weeks.

Other laboratory studies, including blood counts, cold agglutinins, cryoglobulins, and general chemistry studies, are usually normal.

Differential diagnosis

The history of cold exposure in an otherwise healthy infant will help to distinguish cold panniculitis from other causes of subcutaneous nodules. Clinical lesions of SCFN can overlap with those of cold panniculitis. Although a skin biopsy is not usually necessary to distinguish these two disorders, the distribution of nodules and histological changes is usually distinctive. Cellulitis should also be considered in any child with tender red facial nodules. However, the lack of progression of lesions or fever in a healthy-appearing infant is against the diagnosis of infection.

Post-steroid panniculitis can be clinically indistinguishable from cold panniculitis.⁴⁶ Subcutaneous nodules or plaques appear on the cheeks of infants within 2 weeks of rapidly discontinuing high-dose systemic steroids after a prolonged course. A biopsy reveals granulomatous inflammation in the fat lobules and needle-shaped clefts within histiocytes identical to those of SCFN. However, in a child with a typical history, a biopsy is unnecessary, and nodules resolve over a period of months without treatment.

Treatment and course

Although skin lesions are self-limiting and no treatment is recommended, early recognition of cold panniculitis is important to prevent unnecessary parental anxiety or laboratory studies. Nodules heal in 1–3 weeks without scarring.

Mechanical trauma

Cutaneous findings

Firm, subcutaneous nodules may follow blunt trauma to the skin, especially in areas prone to trauma where the fat is in close

proximity to the underlying bone.⁴⁷ This occurs most commonly on the cheeks in children between 6 and 12 years old. However, nodules can also develop in infants and over other bony prominences after accidental or deliberate injury.

Diagnosis

Traumatic fat injury should be considered in any child with subcutaneous nodules over injury-prone areas. Skin biopsies will demonstrate fat necrosis with granulomatous inflammation. Late histologic changes may include fibrosis, small fat cysts, and dystrophic calcification.⁴⁸ However, a biopsy is usually not necessary.

Treatment and course

Nodules slowly resolve over 6–12 months without treatment. In some patients localized lipoatrophy can lead to a depression with normal overlying epidermis and dermis.

Injection-site granuloma

Cutaneous findings

Firm, asymptomatic, itchy, or tender, subcutaneous nodules commonly appear 1–2 days after vaccinations in the buttocks or thighs in infants, and in the deltoid area in older children and adults.^{49,50} Although lesions occasionally result from direct trauma to the subcutaneous tissue when the needle is accidentally placed in the fat, some patients develop aluminum granulomas when an aluminum-adsorbed vaccine is used.

Diagnosis

The diagnosis is apparent when one or several nodules develop in a vaccination injection site. Skin biopsies demonstrate characteristic findings, including lymphoid follicles with germinal centers and a dense surrounding infiltrate of lymphocytes, histiocytes, plasma cells, and eosinophils. Staining for aluminum is also positive, confirming the diagnosis.⁴⁹

Differential diagnosis

Other foreign material injected into the skin can produce panniculitis, with nodule formation and fat necrosis. This can occur with certain medications and intravenous fluid extravasation.⁵¹ Munchausen syndrome by proxy should be considered when recurrent panniculitis with associated cellulitis and/or ulceration occurs in an otherwise healthy infant without a clear diagnosis.

Treatment and course

Injection-site granulomas usually resolve without scarring within 2 weeks, although they can last much longer. Occasionally, liponecrosis leads to ulceration and/or lipoatrophy, with persistent dimpling of the skin.

Infectious panniculitis

Although this entity usually occurs in immunocompromised adults, there are rare reports of affected children in the pediatric and infectious disease literature.^{52–54} In infants, infectious panniculitis can occur as an extension of primary cutaneous infection, direct hematogenous dissemination to fat, or inoculation from a penetrating wound or indwelling catheter.²⁰



Figure 27.6 Multiple nodules of panniculitis in an infant with *Escherichia coli* sepsis.

Cutaneous findings

Septic emboli produce tender, red, subcutaneous nodules that are usually confined to one area, such as a portion of an extremity, but widespread dissemination can occur (Fig. 27.6).

In primary cutaneous infection, superficial tissue destruction by the invading organism and ischemia from invasion of local blood vessels and lymphatics leads to necrosis and ulceration of the skin and deeper soft tissue structures.

Extracutaneous findings

Infected children are febrile, irritable, and appear ill. There may be other signs of systemic infection or sepsis. Although infectious panniculitis is more common in immunocompromised individuals,⁵⁵ it has rarely been reported in immunocompetent children.⁵²

Etiology and pathogenesis

Infectious panniculitis has been associated with Gram-positive (*Staphylococcus aureus*, *S. epidermidis*, *Streptococcus* sp.) and Gram-negative (*Pseudomonas* sp., *Klebsiella* sp., *Fusobacterium*, *Fusarium*) bacteria, fungi (*Candida* sp., *Nocardia* sp.), and atypical mycobacteria.

Diagnosis

Skin biopsies from subcutaneous nodules reveal a mixed septal-lobular panniculitis with infiltration by neutrophils.^{52,53,55} Special stains demonstrate organisms scattered throughout fat lobules. Blood cultures and cultures of other body fluids may also be positive.

Differential diagnosis

Other conditions to be considered in the setting of possible panniculitis associated with fever include erythema nodosum, Henoch-Schönlein purpura (HSP), and cellulitis. The most difficult of these to exclude is erythema nodosum, an immunologically mediated phenomenon commonly associated with streptococcal and other infections. In erythema nodosum, the panniculitis occurs primarily in the fat septa, and the infecting organisms are not found in the skin nodules. HSP is not usually associated with fever, and skin biopsy shows leukocytoclastic vasculitis.



Figure 27.7 Lipoma of the forehead in a young infant.

Treatment and course

Treatment should be directed against the specific organism. Skin biopsy for pathology and cultures, blood cultures, and other appropriate cultures will hopefully identify a specific organism and direct antibiotic and/or antifungal therapy.

Tumors of fat

Tumors of fat include a number of neoplasms and hamartomatous malformations. A specific diagnosis is important to distinguish between those disorders with isolated cutaneous findings and those with systemic implications.

LIPOMA

Cutaneous findings

Although lipomas represent the most common tumor of the mesenchyme in adults, they are rare in infants and account for <5% of tumors of childhood. Lipomas are soft, rounded or lobulated, mobile, slightly compressible, subcutaneous tumors with smooth margins (Fig. 27.7). Lumbosacral lipomas are usually congenital and occur in conjunction with intraspinal lipomas and anomalies of the spine (Fig. 27.8).⁵⁶⁻⁵⁹ They are often softer and less discrete than lipomas found in other sites. When infants and young children present with multiple lipomas, especially when the lesions are congenital, the clinician should do a careful medical and cutaneous examination to exclude rare underlying systemic disorders.

Extracutaneous findings

In 1967, Lassman and James⁵⁶ described 26 cases of lumbosacral lipomas associated with laminar defects on X-ray and spinal anomalies at surgery. The recognition of lipomas as markers of underlying spinal dysraphism has been re-emphasized by a number of investigators.⁵⁶⁻⁵⁹ Conversely, most cases of intraspinal lipoma are associated with congenital lumbosacral cutaneous markers, including lipoma, myelocele closure scar, hairy patch, vascular lesions, and dimpling (see also Chapter 9).⁵⁸



Figure 27.8 Lumbosacral lipoma associated with lipoma of the cord. Note the deviation of the gluteal cleft.

A sporadic, nonhereditary, genetic, mosaic disorder with lipomas and segmental fat hypoplasia was recently described with the acronym CLOVE syndrome (congenital lipomatous overgrowth, vascular malformations, and epidermal nevi).⁶⁰ This disorder is characterized by linear epidermal nevi, progressive, complex, and mixed truncal vascular malformations (typically combined venous lymphatic malformations), dysregulation of adipose tissue, and enlarged bony structures without progressive bony overgrowth. Heterogeneous central system structural anomalies have also been described. In 2012 investigators reported a distinct somatic activating mutation in the *PIK3CA* gene as the cause of CLOVE syndrome.⁶¹ When CLOVE syndrome is suspected, a systemic evaluation and imaging studies should be directed by clinical findings. CLOVE syndrome should be distinguished from PTEN-associated lipomatous disorders including Proteus syndrome, Bannayan–Riley–Ruvalcaba syndrome, and Cowden syndrome which share a number of clinical findings with CLOVE.^{62,63} Children with PTEN-associated disorders are also at risk for the development of malignant tumors in adulthood and should be screened accordingly.⁶³

Diagnosis

The presence of a soft, spongy congenital mass in the lumbosacral area is characteristic, and requires a radioimaging evaluation to exclude anomalies of the underlying cord and bony spine. Ultrasound is a reliable noninvasive screening tool for infants during the first 6 months of life. In older children, or when the findings are equivocal on ultrasound, MRI may be required.^{64,65} Histologic findings are typical of lipomas in other sites and show mature adipocytes within a thin connective tissue capsule.

Treatment, course, and management

Although the need for surgical management of intraspinal lipomas associated with lumbosacral lipomas is controversial, it should be recognized that the development of neurologic impairment can be delayed for years.^{56–59} Unfortunately, many patients present in later childhood and adolescence with neurologic defects in the lower extremities, including weakness and foot deformities. Consequently, immediate neurosurgical evaluation and long-term neurologic follow-up are required.

NEVUS LIPOMATOSUS CUTANEUS SUPERFICIALIS

Nevus lipomatosus cutaneus superficialis (NLCS) is a malformation of the subcutaneous tissue consisting of multiple or solitary papules, usually occurring on the lower trunk, buttocks, or upper thighs.^{66–69} Based on the paucity of reports, NLCS is either rare or underdiagnosed. In 1921, Hoffmann and Zurhelle⁶⁹ described the original case of a 25-year-old man with multiple papules on the left buttock. In 1975, Jones and colleagues⁷⁰ summarized the findings of an additional 40 cases subsequently reported in the literature, and 20 of their own patients. A number of other reports have expanded our understanding of the clinical expression and pathogenesis of NLCS.

Cutaneous findings

Most patients report that lesions were present at birth or appeared in the first two decades of life.^{66–69} However, a number of reports suggest that appearance of lesions may be delayed until the third to fifth decades of life.⁷¹ NLCS typically presents as multiple, soft, skin-colored to yellowish lobules that may coalesce into plaques with a cerebriform surface. Unilateral involvement of the buttock is most common, but plaques may extend to the adjacent skin of the upper thigh or lower back. Lesions may be confined to the upper thigh, lower back, hip, or abdomen. Usually lesions do not cross the midline, but bilateral involvement of opposing surfaces of the buttocks has been reported. Once formed, papules usually remain stable. However, new lobules may develop slowly for decades, and recurrent lesions after excision or progression may be associated with infiltration of the underlying muscle.⁷²

Solitary nevi have been described at various sites, including the scalp, ear, and neck, but these lesions probably represent fibromas or polypoid fibrolipomas rather than true NLCS.

Extracutaneous findings

NLCS is not usually associated with extracutaneous findings.^{66–69} Cases reported with bony, dental, and other anomalies probably represent focal dermal hypoplasia (Goltz syndrome), which can be confused clinically and histologically with NLCS. However, there are several reports of NLCS associated with pigment anomalies, including café-au-lait spots and hypopigmented macules.

Etiology and pathogenesis

Although the origin of NLCS is unclear, electron microscopic studies support the hypothesis of several investigators that the hamartomatous lesion arises from pluripotential vascular elements in the dermis.⁶⁷ The presence of varying amounts of other connective tissue components also suggests a relationship with connective tissue nevi.

Diagnosis

Although the clinical appearance of NLCS varies, the presence of typical nodules and plaques in the pelvic girdle region should suggest the diagnosis. Histopathology shows some hyperkeratosis and acanthosis of the epidermis and a marked increase in mature fat cells throughout the dermis.^{67,69} Adipocytes are most prominent in the reticular dermis, where they are arranged in clusters and interspersed by broad, interwoven, collagen bundles. However, they may extend into the papillary dermis, and the distinction between the dermis and subcutaneous fat

may be poorly defined. Although the remainder of the dermis often appears normal, other connective tissue anomalies, including thickening of collagen and elastic fibers, and increased numbers of fibroblasts and blood vessels with a perivascular mononuclear infiltrate, may also develop.

Differential diagnosis

The varying clinical findings explain the wide range of clinical diagnoses suspected before skin biopsy. These include pigmented nevi, supernumerary nipples, lipomas, neurofibromas, connective tissue nevi, sebaceous nevi, epidermal nevi, and warts.

Encephalocraniocutaneous lipomatosis and congenital diffuse lipomatosis ('Michelin tire baby') may represent distinctive variants of NLCS (see below).

Treatment, course, and management

Although new lobules may develop in adolescence and adult life, NLCS is usually static and not associated with pain, pruritus, or other symptoms. Consequently, treatment is not necessary, but surgical excision, particularly for small lesions, gives a good cosmetic result. Moreover, excision should be considered in lesions that demonstrate progressive growth.⁷³

ENCEPHALOCRANIOCUTANEOUS LIPOMATOSIS

In encephalocraniocutaneous lipomatosis (ECL), unilateral cerebral malformations are associated with ipsilateral scalp, face, and eye lesions.⁷⁴ Since the first description of this congenital neurocutaneous disorder in 1970 by Haberland and Perou,⁷⁵ at least 60 additional cases with similar clinical and histologic findings have been reported.^{76–80}

Cutaneous findings

Soft, spongy, hairless, pink-yellowish tumors characteristically involve the scalp, often in a linear configuration, but may extend to the legs and paravertebral area.^{74–80} On the scalp, these lesions are sometimes referred to as nevus psiloliparus (see [Chapter 31](#)).⁷⁶ Although lesions are usually unilateral, bilateral involvement has been reported. Papular and polypoid nodules, often contiguous to the scalp lesions, are constant features on the face of affected infants. Atrophic hairless patches may also be present on the scalp and face.⁷⁴

Extracutaneous findings

Characteristic papules and nodules on the bulbar conjunctivae show histologic features of desmoid tumors.⁷⁴ Anomalies of the hyaloid vessel system, lens, and cornea are also common.⁸¹

Cerebral defects are usually ipsilateral to the main cutaneous scalp lesions and include ventricular dilatation and cerebral atrophy.^{74,82} Other anomalies, including arachnoid cyst, pontocerebellar lipoma, porencephaly, agenesis of the corpus callosum, and paramedullary lipomas, have also been described.

Affected children seem to be prone to the development of benign osseous lesions, including ossifying fibromas, odontomas, osteomas, and fibrous dysplasia.⁷⁹ Recently, low-grade gliomas⁷⁹ and intracranial vascular malformations have also been described.⁸⁰

Etiology and pathogenesis

There is no evidence of familial transmission or chromosomal aberration, and all cases have been sporadic. Happle⁸³ proposed

that ECL might be caused by a lethal autosomal mutation that survives in the mosaic state.

Diagnosis

Biopsies of the cutaneous nodules show normal epidermis overlying a dermis with irregularly shaped collagen fibers that extend into the subcutis and form large fibrous septa associated with increased amounts of fat.^{74–78} These histologic features typical of fibrolipoma seen in children with characteristic cutaneous, ocular, and cerebral features should suggest the diagnosis of ECL.

Differential diagnosis

The clinical features of ECL may overlap with those of focal dermal hypoplasia (Goltz syndrome), oculoauricular vertebral dysplasia (Goldenhar syndrome), Schimmelpenning syndrome, oculocerebrocutaneous (Dellman) syndrome, Proteus syndrome, and the epidermal nevus syndrome. However, careful analysis of clinical and histologic features will help to distinguish these neurocutaneous genodermatoses.

Treatment and course

The care of affected children is determined by neurologic symptoms, which range from normal to global neurodevelopmental retardation, unilateral spasticity, and mental retardation.⁷⁴ Seizures are variable and may develop later in childhood. Moreover, the severity of neurologic symptoms does not seem to correlate with the extent of cutaneous involvement. Ocular and cutaneous lesions appear to be static and amenable to surgical repair. Children without clinical evidence of neurologic involvement should be screened for occult spinal anomalies.⁸²

CONGENITAL DIFFUSE LIPOMATOSIS

Congenital diffuse lipomatosis (Michelin tire baby) was initially referred to by Ross in 1969,⁸⁴ who described a child with ringed creases of the skin reminiscent of the mascot of the French tire manufacturer Michelin. Since then, a number of cases of this rare hamartomatous disorder have been reported, demonstrating the variability of clinical and histologic findings.^{84–89}

Cutaneous findings

Symmetric ringed creases of the extremities may be associated with hirsutism of the arms, legs, shoulders, and buttocks ([Fig. 27.9](#)).^{84–88} The palmar and plantar skin may also demonstrate excessive folding. Although scalp hair is usually normal, long curled eyelashes and thick eyebrows are typical.

Extracutaneous findings

Although affected children may be otherwise normal, a number of anomalies have been reported.^{84–88} Facial dysmorphisms have included epicanthal folds, hypertelorism, an antimongoloid slant to the eyes, a flat nasal bridge, and low-set ears. Variable oral anomalies, including cleft lip and palate, a high-arched palate, dental hypoplasia, and micrognathia, are common. Orthopedic defects such as rocker-bottom feet, metatarsus abductus, coxa valga, genu valgus, overlapping of toes, and pectus excavatum may require surgical intervention. Psychomotor delay and the development of seizures are also variable.



Figure 27.9 Multiple ringed creases of congenital diffuse lipomatosis. (Reproduced with permission from Novice FM, Collison DW, Burgdorf WHC, Esterly NB. *Handbook of genetic skin disorders*. Philadelphia: WB Saunders; 1994.)

Etiology and pathogenesis

Although no specific chromosomal abnormality has been identified in congenital diffuse lipomatosis, autosomal dominant inheritance has been noted in two families in which the cutaneous findings occurred as isolated defects.⁸⁷ In two other patients with multiple associated anomalies, unrelated cytogenetic defects were found.⁸⁵ Further studies may help to detect a Michelin tire baby gene, although this syndrome may represent disparate disorders with similar phenotypic expression.

Diagnosis

Skin biopsies from the extremities of affected children have shown changes in the dermis consistent with nevus lipomatosus cutaneous superficialis or smooth muscle hamartoma.^{85,86} A report in which histopathology showed fragmented elastic fibers and decreased deposition of elastin on electron microscopy suggests that some cases may result from a primary defect in elastic fibers.⁸⁶

Differential diagnosis

Although congenital diffuse lipomatosis may be confused histologically with localized smooth muscle hamartoma, Becker nevus, and nevus lipomatosus cutaneous superficialis, the diffuse, symmetric, and dramatic cutaneous findings are distinctive.

Treatment, course, and management

Management of affected individuals depends on the presence of associated anomalies. Clinicians should look carefully for oral and orthopedic anomalies, which may require early surgical intervention. Neurodevelopmental parameters will also require long-term follow-up.



Figure 27.10 Congenital pedal papules.

CONGENITAL PEDAL PAPULES

Congenital papules or nodules of the plantar surface of the feet have been described under a variety of names, including congenital pedal papules, congenital piezogenic-like papules, plantar fibromatosis of the heel, 'podalic papules of the newborn,' and precalcaneous fibrolipomatous hamartoma.⁹⁰⁻⁹³

Cutaneous findings

Pedal nodules are asymptomatic, symmetric, flesh-colored nodules of the medial plantar surface of the feet, generally 0.5–1.5 cm in size (Fig. 27.10). They are ill-defined and may go unnoticed by caregivers. Lesions undergo minimal change over time, though proportionate growth may be seen.

Etiology and pathogenesis

The pathogenesis is uncertain. Possible etiologies include a hamartomatous condition with incomplete regression of fetal tissue or a developmental defect in the plantar aponeurosis. The nodules may occur in a familial pattern.⁹⁴ Histopathology displays increased mature adipocytes in the mid and deep dermis within fibrous sheaths.

Diagnosis and differential diagnosis

The diagnosis is a clinical one. Differential diagnosis includes piezogenic papules seen on the lateral surface of the feet in older children, fibrous hamartoma of infancy, and aponeurotic fibroma.

Treatment and course

Although the natural history is not fully known, lesions seem to persist over time. Treatment is unnecessary.

LIPOBLASTOMA AND LIPOBLASTOMATOSIS

Lipoblastoma is a term first used by Jaffe⁹⁵ in 1926 to describe recurrent fatty tumors of the groin in infants and young children. Van Meurs⁹⁶ subsequently wrote of his experience with an infant with a lipomatous tumor in the right axilla that required four surgeries over a 2-year period before she was free of recurrence. Histologic changes from biopsies over the 2-year period in Van Meurs' case demonstrated maturation from a tumor comprised primarily of lipoblasts to a mature lipoma. In 1973 Chung and Enzinger⁹⁷ reported a large series of lipomatous tumors in infancy and proposed that the term lipoblastoma be used to describe the well-encapsulated variant and that lipoblastomatosis be reserved for unencapsulated infiltrating lesions.



Figure 27.11 Lipoblastomatosis involving the entire leg and foot, present from birth.

Cutaneous findings

Clinically, the tumors are soft, subcutaneous or deep, soft tissue masses ranging in size from 1 to 12 cm in diameter.^{98–101} Although cases have been diagnosed in children as old as 10 years, most appear before 3 years of age, and congenital tumors are common. In a recent review of 410 cases, 68% were encapsulated and 32% had a diffuse growth pattern; 80% were on the trunk and extremities (Fig. 27.11), 17% head and neck, and 5% face and head. However, unusual sites, including the parotid gland, mediastinum, and tonsils, have been reported. Some 98% were under 20 years old and 78% under 3, and there was a 1.5:1 male to female predominance.¹⁰¹

Etiology and pathogenesis

Although the cause of lipoblastoma is unknown, several reports demonstrate an association with rearrangements of chromosome band 8q 11–13 which targets the gene *PLAG1*.^{101,102} Electron microscopic findings suggest a close resemblance to human fetal adipose tissue.¹⁰³ Some investigators propose that lipoblastoma results from the continued proliferation of fetal lipoblasts in the postnatal period. This is supported by observations of histologic maturation of adipose cells in recurrent tumors.

Diagnosis

Histologically, lipoblastoma is encapsulated or well circumscribed, whereas in lipoblastomatosis the tumor infiltrates surrounding normal structures.^{97–99,101} The diagnostic feature is the presence of lobules of mature and immature fat cells, primitive mesenchymal cells, and lipoblasts with varying degrees of differentiation. The lobules are separated by fibrous septa

containing small blood vessels, hyaline collagen, and fibroblasts. There is no evidence of atypia, and mitotic figures are rare.

Differential diagnosis

Lipoblastomatosis should be differentiated from liposarcoma, an exceedingly rare tumor in children under 10 years of age.⁹⁹ Although histologic distinction is occasionally difficult, the lack of cytologic atypia and mitotic figures and the presence of a uniform growth pattern and extensive lobulation favor lipoblastoma. MRI features showing enhancing cystic lesions and enhancing soft tissue nodules may help to distinguish lipoblastoma from other lipomatous tumors in young children.¹⁰⁴

Treatment and course

Encapsulated tumors represent the majority of lesions and generally respond well to simple excision. However, in some series lipoblastomatosis accounts for nearly a third of cases. Metastases do not occur, but recurrences are common. Although extensive infiltration into local muscle and fascial structures precludes complete excision, in most cases maturation of recurrent tumor results in a favorable outcome.

Lipodystrophies

The lipodystrophies are a rare group of disorders characterized by complete or partial loss of fat. The congenital variants are inherited in an autosomal recessive pattern and express variable abnormalities in carbohydrate and lipid metabolism and insulin resistance.

LEPRECHAUNISM

Donohue and Uchida^{105,106} were the first to describe this rare syndrome when they reported their observations on two sisters of consanguineous parents, with intrauterine growth retardation, gnome-like facies, and severe endocrine dysfunction evidenced by emaciation, enlargement of the breasts and clitoris, and histologic changes in the ovaries, pancreas, and breasts.¹⁰⁷ Leprechaunism was the term applied to the elfin facial features and poor growth characteristic of this disorder.

The incidence of this autosomal recessive disorder has been estimated at 1 in 4 million live births, and the prevalence of the carrier state as at least 1 in 1000 individuals.¹⁰⁸

Cutaneous findings

In a review of 31 patients with leprechaunism reported since the original description by Donohue in 1948, Elsas and colleagues¹⁰⁹ summarized the clinical findings, including severe growth retardation; an elfin face with large, protuberant, low-set ears; depressed nasal bridge with a broad nasal tip and flared nares; thick lips; distended abdomen; relatively large hands, feet, nipples, and genitalia; and abnormal skin with hyperpigmentation, café-au-lait spots, hypertrichosis, acanthosis nigricans, pachyderma, and decreased subcutaneous fat (Fig. 27.12).^{109–111} The virtual absence of fat gives a cachectic appearance, with wrinkled skin hanging loosely over the skeletal frame.

Etiology and pathogenesis

Initially leprechaunism was identified as a primary endocrinologic disorder because of the associated cystic changes of the gonads and hyperplasia of the islet cells of the pancreas. In the 1970s and 1980s, laboratory advances led to the identification



Figure 27.12 Infant with leprechaunism.

of severe insulin resistance resulting from a genetic defect of the insulin receptor system in infants with leprechaunism.^{109,110} Using molecular genetic techniques, the first defect in the insulin receptor gene was discovered in a child with leprechaunism in 1988.¹¹² Subsequently, multiple mutations have been described, indicating that there is great genetic heterogeneity in this disorder.¹¹³ Overactivation of insulin-like growth factor-1 (IGF-1) by high levels of insulin and lack of functional insulin receptors in a number of organ systems lead to growth failure, lipodystrophy, and other cutaneous findings.

Diagnosis

Diagnosis can be made by identifying characteristic clinical, biochemical (fasting hypoglycemia, postprandial hyperglycemia, and extreme hyperinsulinism), and genetic findings.¹¹³ The diagnosis can be confirmed by DNA analysis of fibroblasts grown in culture from skin biopsies from affected infants. Specific mutations in the insulin receptor gene can be identified. Prenatal diagnosis is possible by similar evaluation of chorionic villus biopsy specimens.

Differential diagnosis

Leprechaunism shares many features with congenital total lipodystrophy, including insulin resistance, absence of subcutaneous fat, acanthosis nigricans, and hyperpigmentation. The differential also includes Rabson–Mendenhall syndrome, and HAIR-AN syndrome.¹¹⁴ However, the elfin facies, wrinkled skin, and other cutaneous markers are distinctive.

Treatment and course

Postnatal growth is invariably poor, and affected children are severely motor and mentally retarded. Infants rarely survive beyond the first few months of life unless they have some residual insulin receptor function. Stabilization of blood glucose during early infancy is critical for survival. Recent data suggest

that the administration of recombinant IGF1 may be effective in managing the primary defect.¹¹⁵

CONGENITAL GENERALIZED LIPODYSTROPHY (SEIP–BERARDINELLI SYNDROME)

Congenital generalized lipodystrophy (CGL) was first described by Berardinelli in 1954, and in greater detail by Seip in 1959.^{116,117} In 1996, Seip published a follow-up study of the original patients and summarized the findings from over 90 cases reported in the literature.¹¹⁸ Over the last decade, the discovery of genetic markers has resulted in the identification of four distinctive CGL variants.¹¹⁹

Cutaneous findings

A partial to complete absence of subcutaneous fat and marked muscular hypertrophy are evident at birth and persist through adolescence. The findings at birth are most dramatic in infants with Berardinelli–Seip syndrome (CGL2). The skin tends to become coarse, particularly in boys, and patients often develop warty fibromas on the upper half of the body.^{107,116,118} Acanthosis nigricans develops to a variable degree in early childhood but disappears in adolescence. Excessive, curly scalp hair and hypertrichosis are also common.

Extracutaneous features

An anabolic state develops, with increased height velocity, advanced bone and dental age, muscular hypertrophy, masculine body build, acromegaly stigmata, organomegaly, and enlarged genitals.^{116–118} Growth velocity is already advanced at birth and continues throughout childhood. The absence of facial fat pads and enlarged muscles gives adolescent girls a female ‘body-builder’ look.

Patients tend to be hypermetabolic with a voracious appetite, increased energy consumption, and associated hyperhidrosis and decreased heat tolerance. Cardiac muscle hypertrophy is also present at birth and may result in progressive hypertrophic cardiomyopathy with decrease in cardiac function. Most patients with CGL demonstrate mild to moderate developmental delay and mental retardation.

Infants with CGL1 lack metabolically active fat but retain mechanical adipose tissue (e.g., foot and finger pads, bone marrow). In CGL3, patients demonstrate short stature, and vitamin D resistance, and CGL4 infants present with congenital myopathy, pyloric stenosis, and cardiomyopathy.¹¹⁹

Etiology and pathogenesis

Although the clinical findings in CGL disorders overlap considerably, the identification of four distinct genetic mutations has allowed for the definition of a number of variants.^{119,120} Most affected children have CGL1 or CGL2 (Berardinelli–Seip syndrome). CGL1 is associated with a mutation in the *AGPAT2* gene, which is necessary for the production of key enzymes required for biosynthesis of triglycerides and phospholipids. CGL2 results from mutations in the *BSCL2* gene which encodes seipin, which plays a role in the fusion of small lipid droplets and adipose differentiation. *CAVI* mutations in CGL3 and *PTRF* mutations in CGL4 result in defects in adipose membranes.

Diagnosis

This is a well-characterized disorder inherited in an autosomal recessive fashion, with clinical, metabolic, and genetic features

that allow for diagnosis at birth. Metabolic features include insulin resistance, hyperinsulinemia, hypertriglyceridemia, and nonketotic diabetes. Skin biopsies demonstrate a marked decrease in adipocyte size and number.¹¹⁸ Unlike the subcutaneous fat, glycogen and triglycerides are abundant in the liver, where variable amounts of connective tissue with liver cirrhosis have been noted. Hypertriglyceridemia varies from patient to patient, but tends to increase at puberty and with increased dietary fat consumption. In childhood, glucose and insulin levels tend to be normal except with large glucose challenges. However, at or shortly after puberty, glucose metabolism deteriorates, with the development of clinical diabetes with hyperinsulinemia, elevated serum glucose, and glycosuria. When clinical and metabolic findings suggest a diagnosis of CGL, the diagnosis can be confirmed with genetic markers.

Differential diagnosis

CGL can be distinguished from other lipodystrophies by the characteristic congenital onset and associated clinical, metabolic, and genetic findings. CGL can also be distinguished from neonatal progeroid syndrome, which presents with generalized decreased subcutaneous fat, by the presence of increased buttock fat, absence of the typical CGL metabolic findings and the presence of progeroid features including sparse scalp hair, prominent scalp veins, hypoplastic facial bones, and convex nasal bridge. Neonatal progeroid syndrome, described in the late 1970s by Wiedemann and Rautenstrauch is inherited as an autosomal recessive disorder but the genetic marker has not yet been identified. However, investigators have suggested that a defect in biosynthesis of proteins in the nucleus may be involved.¹²¹

Treatment and course

Treatment is complex and should emphasize dietary measures to control energy consumption, hyperglycemia, and hypertriglyceridemia.¹¹⁸ Appetite suppressants have been used with some success. Therapy is further complicated by moderate to severe mental retardation in most individuals with CGL. Despite therapy, many patients die in childhood of liver cirrhosis or associated complications and/or cardiomyopathy.

CONGENITAL DISORDERS OF GLYCOSYLATION (CDG)

CDG, previously known as carbohydrate-deficient glycoprotein syndrome (CDGS), represents a heterogeneous group of disorders, which all share clinical features that result from a defect in the synthesis of N-linked oligosaccharides.^{122–124} During the last decade the discovery of a number of genetic defects has resulted in the categorization of type 1 and type 2 CDG. Type 1 disorders are the most common and usually associated with congenital onset.¹²⁵

This entity was first recognized by Jaeken and colleagues in 1980,¹²⁶ who reported monozygotic twins with psychomotor retardation, increased CSF protein, delayed nerve conduction velocity, thyroxine-binding deficiency, and increased serum arylsulfatase A activity. Carbohydrate analysis of a number of subsequent patients resulted in identification of the common defect in N-linked glycoproteins.

Cutaneous findings

Dysmorphic features typical of CDG type 1 appear in infancy, including inverted nipples and an abnormal distribution of fat

over the suprapubic region and labia majora.^{122–124} Peculiar fat pads, which tend to disappear in later childhood, are noted on the superior lateral portion of the buttocks. Lipoatrophy can be marked on the rest of the buttocks, and lipoatrophic streaks often extend down the legs. Variable facial dysmorphisms include a high nasal bridge, prominent jaw, and large pinnae.

Extracutaneous findings

Neurologic features include hypotonia, hyporeflexia, and alternating esotropia.¹¹⁸ Infants often suck poorly and present with feeding difficulties. Even when nutritional intake is good, lipoatrophy gives many children an emaciated appearance. Although most infants are full term and appropriate weight for gestational age, developmental delay, and failure to thrive usually occur by 3 months of age.

Significant coagulopathy may result in stroke-like episodes, and hepatomegaly with hepatic dysfunction is common. Renal cysts, pericardial effusions, pericardial tamponade, and hypertrophic obstructive cardiomyopathy have been reported.

Although the central nervous system involvement tends to be static, musculoskeletal complications, including muscular atrophy, contractures, and spinal deformities, progress in later childhood and adulthood. In females, defective peptide hormone glycosylation results in hypogonadotrophic hypogonadism with failure to undergo pubertal sexual development. Males are virilized at puberty, but may exhibit decreased testicular volume. Other endocrinologic findings result from hyperglycemia-induced growth hormone release, hyperprolactinemia, and insulin resistance.

Etiology and pathogenesis

In both type 1 and type 2 disorders, multiple variants based on specific genetic defects have been named based on the chronological order in which they were discovered. For type 1 and 2 there are groups a–o and a–h, respectively. These autosomal dominant inherited disorders have been tied to specific defects in N-linked oligosaccharide synthesis.¹²⁵

Diagnosis

Typical clinical features seen in association with the presence of abnormally glycosylated serum proteins, typically transferrin detected by cathodal migration on serum isoelectric focusing, may allow for diagnosis in the neonatal period. This can be confirmed by specific genetic analysis.

Prenatal diagnosis can be made with mutational studies along with enzymatic analysis of amniotic fluid or chorionic villus cells.^{125,127}

Differential diagnosis

Although other lipodystrophies should be considered, the clinical features are usually distinctive. When dysmorphic features are subtle, biochemical studies are required to distinguish CDG from related disorders.

Treatment and course

Supportive treatment is necessary to avoid complications from the central nervous system, as well as ophthalmologic and hematologic manifestations of CDG. Mannose has been used to deal with some of the acute crises of infancy, including intractable seizures, severe coagulopathy, and pericardial effusions, but does not change the dismal prognosis.

FARBER LIPOGRANULOMATOSIS

Farber disease is a rare autosomal recessive disorder of lipid metabolism that usually presents with a fatal course in early infancy.^{124,128,129} Although skin, joint, and laryngeal symptoms associated with neurodegeneration are characteristic, some patients may present with later onset of primarily neurologic findings.

Clinical findings

Tender, red, subcutaneous nodules and swelling appear during the first few weeks of life over joints and areas of trauma, particularly the wrists and ankles. Granulomatous infiltration of the larynx results in a weak, hoarse cry.^{128,129} Infants are usually irritable, and psychomotor retardation is severe. Reticuloendothelial involvement may produce generalized lymphadenopathy and marked hepatosplenomegaly.

Etiology and pathogenesis

In Farber disease, ceramide, a normal intermediate in the metabolism of gangliosides and structurally important sphingolipids and glycolipids, accumulates as a result of a deficiency of lysosomal acid ceramidase.¹²⁸ Variable storage of ceramide occurs in visceral organs and brain white matter.

Diagnosis

The biochemical defect can be demonstrated in kidney, liver, cultured fibroblasts, and leukocytes and specific defects in the

human acid ceramidase gene *ASAH1* can be demonstrated.^{128–130} Prenatal diagnosis is also possible by amniocentesis and chorionic villus sampling for biochemical and genetic analysis.

Differential diagnosis

In the young infant, the diagnosis can usually be made clinically when the classic findings are present. However, when various aspects are missing, Farber disease can be confused with juvenile rheumatoid arthritis, multicentric reticulohistiocytosis, and juvenile hyaline fibromatosis.¹²⁹ Ceramide levels are normal in all of these conditions.

Treatment and course

The clinical course is usually characterized by recurrent fever and pulmonary infiltrates, with death occurring by 2 years of age. Rarely, patients present with later onset of neurologic disease followed by extraneuronal granulomas in skin and viscera. Some patients with little or no involvement of the central nervous system develop normally and survive longer.

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KEY REFERENCES

2. Mitra S, Cove J, Somisetty SK. Subcutaneous fat necrosis in a newborn – an unusual course and review of the literature. *Eur J Pediatr* 2011;170:1085–6.
7. Zifman E, Mouler M, Eliakim A, et al. Subcutaneous fat necrosis and hypercalcemia following therapeutic hypothermia – a patient report and review of the literature. *J Pediatr Endocrinol Metab* 2010;23(11):1185–8.
20. Polcari IC, Stein SL. Panniculitis in children. *Dermatol Ther* 2010;23:356–67.
35. Liu T, McCalmont TH, Frieden IJ, et al. The stiff skin syndrome: case series, differential diagnosis of the stiff skin phenotype, and review of the literature. *Arch Dermatol* 2008;144:1351–9.
54. Douvovianis M, Litman N, Dulau A, et al. Panniculitis, infection, and dermatomyositis: a case and literature review. *Clin Rheumatol* 2009;28(Suppl.):S57–63.
60. Sapp JC, Turner JT, van de Kemp JM, et al. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformation and epidermal nevi (CLOVE syndrome) in 7 patients. *Am J Med Genet A* 2007;143: 2944–58.
72. Jung S-T, Park H-W, Yun SJ. Giant nevus lipomatosis cutaneous superficialis. *J Am Acad Dermatol* 2012;67:e168–70.
107. Musso C, Cochran E, Moran SA, et al. Clinical course of genetic diseases of insulin receptor (type A and Rabson–Mendenhall syndromes): a 30-year prospective. *Medicine (Baltimore)* 2004;83:209–22.
121. Arboleda G, Morales LC, Quintero H, et al. Neonatal progeroid syndrome (Wiedemann–Rautenstrauch syndrome): report of three affected sibs. *Am J Med Genet A* 2011;155A: 1712–15.
125. Woods AG, Woods CW, Snow TM. Congenital disorders of glycosylation. *Adv Neonatal Care* 2012;12:90–5.

REFERENCES

- Holbrook KA. Structure and function of the developing human skin. In: Goldsmith LE, editor. Physiology, biochemistry and molecular biology of the skin. 2nd ed. vol. 1. New York: Oxford University Press; 1991. p. 63.
- Mitra S, Cove J, Somisetty SK. Subcutaneous fat necrosis in a newborn – an unusual course and review of the literature. *Eur J Pediatr* 2011;170:1085–6.
- Akin MA, Akin L, Coban D, et al. Subcutaneous fat necrosis in a newborn; case report. *Fetal Pediatr Pathol* 2011;30:363–9.
- Scales JW, Krowchuk DP, Schwartz RP, et al. An infant with firm fixed plaques. *Arch Dermatol* 1998;134:425–6.
- Fretzin DF, Arias AM. Sclerema neonatorum and subcutaneous fat necrosis of the newborn. *Pediatr Dermatol* 1987;4:112–22.
- Hogeling M, Meddles K, Berk DR, et al. Extensive subcutaneous fat necrosis of the newborn associated with therapeutic hypothermia. *Pediatr Dermatol* 2012;29:59–63.
- Zifman E, Mouler M, Eliakim A, et al. Subcutaneous fat necrosis and hypercalcemia following therapeutic hypothermia – a patient report and review of the literature. *J Pediatr Endocrinol Metab* 2010;23(11):1185–8.
- Rosbotham JL, Johnson A, Haque KN, et al. Painful subcutaneous fat necrosis of the newborn associated with intrapartum use of a calcium channel blocker. *Clin Exp Dermatol* 1998;23:19–21.
- Silverman AK, Michels EH, Rasmussen JE. Subcutaneous fat necrosis in an infant occurring after hypothermic cardiac surgery. *J Am Acad Dermatol* 1986;15:331–6.
- Duhn R, Schoen E, Sui M. Subcutaneous fat necrosis with extensive calcification after hypothermia in two newborn infants. *Pediatrics* 1968;41:661–4.
- Hicks MJ, Levy ML, Alexander J, et al. Subcutaneous fat necrosis of the newborn and hypercalcemia: A case report and review of the literature. *Pediatr Dermatol* 1993;10:271–6.
- Fernandez-Lopez E, Garcia-Dorado J, de Unamuno P, et al. Subcutaneous fat necrosis of the newborn and idiopathic hypercalcemia. *Dermatology* 1990;180:250–4.
- Rice AM, Rivkees SA. Etidronate therapy for hypercalcemia in subcutaneous fat necrosis of the newborn. *J Pediatr* 1999;134:349–51.
- Schubert PT, Razack R, Vermaak A, et al. Fine-needle aspiration cytology of subcutaneous fat necrosis of the newborn: the cytology spectrum with review of the literature. *Diagn Cytopathol* 2012;40(3):245–7.
- Akin MA, Akin L, Sarico D, et al. Follow-up during infancy of newborns diagnosed with subcutaneous fat necrosis. *J Clin Res Pediatr Endocrinol* 2011;3(4):216–18.
- Karochristou K, Siahianidou T, Kakouvon-Tsivitanidou T, et al. Subcutaneous fat necrosis of the newborn associated with hypocalcemia in a neonate. *J Perinatol* 2006;26:64–6.
- Tran JT, Sheth AP. Complications of subcutaneous fat necrosis of the newborn: a case report and review of the literature. *Pediatr Dermatol* 2003;20:257–61.
- Zeb A, Rosenberg RE, Ahmed NU, et al. Risk factors for scleredema neonatorum in preterm infants in Bangladesh. *Pediatr Infect Dis J* 2009;28(5):435–8.
- Christi MJ, Saha S, Roy CN, et al. Predictors of mortality in infants with sclerema presenting to the Centre for Diarrhoeal Disease, Dhaka. *Ann Trop Paediatr* 2009;29(1):45–50.
- Polcari IC, Stein SL. Panniculitis in children. *Dermatol Ther* 2010;23:356–67.
- Zeb A, Darmstadt GL. Sclerema neonatorum: a review of the nomenclature, clinical presentation, histologic features, and differential diagnoses and management. *J Perinatol* 2008;28:453–60.
- Kellum RE, Ray TL, Brown GR. Sclerema neonatorum. *Arch Dermatol* 1968;97:372–6.
- Horsfield MB, Yardley H. Sclerema neonatorum. *J Invest Dermatol* 1965;44:326–32.
- Warwick WJ, Ruttenberg HD, Quie PG. Sclerema neonatorum, a sign, not a disease. *JAMA* 1963;184:680.
- Gupta AK, Shashi S, Mohon M, et al. Epidemiology of *Pseudomonas aeruginosa* infection in a nursery intensive care unit. *J Trop Pediatr* 1993;39:32–6.
- Gupta P, Murali MV, Furidi MM, et al. Clinical profile of *Klebsiella* septicemia in neonates. *Indian J Pediatr* 1993;60:568–72.
- Zeck P, Madden EM. Sclerema neonatorum of both internal and external adipose tissue. *Arch Pathol* 1946;41:166.
- Esterly NB, McKusick VA. Stiff skin syndrome. *Pediatrics* 1971;47:360–9.
- Jablonska S, Groniowski J, Krieg T, et al. Congenital fascial dystrophy – a noninflammatory disease of fascia: the stiff skin syndrome. *Pediatr Dermatol* 1984;2:87–97.
- Caspary P, Costa F, Souza PR, et al. Familial localized stiff skin syndrome. *Int J Dermatol* 2010;49:842–8.
- Loeys BL, Gerber EE, Riegert-Johnson D, et al. Mutations in fibrillin-1 cause congenital scleroderma: stiff skin syndrome. *Sci Transl Med* 2010;2(23):23ra20. doi: 10.1126/scitranslmed.3000488.
- Kikuchi I, Inoue S, Hamada K, et al. Stiff skin syndrome. *Pediatr Dermatol* 1985;3:48–53.
- Fidzianska A, Jablonska S. Congenital fascial dystrophy: abnormal composition of the fascia. *J Am Acad Dermatol* 2000;43:797–802.
- Gilaberte Y, Sainz-de-Santamaria MC, Farcia-Latas FJ, et al. Stiff skin syndrome: a case report and review of the literature. *Dermatology* 1995;190:148–51.
- Liu T, McCalmont TH, Frieden IJ, et al. The stiff skin syndrome: case series, differential diagnosis of the stiff skin phenotype, and review of the literature. *Arch Dermatol* 2008;144:1351–9.
- Jablonska S, Schubety J, Kikuchi I. Congenital fascial dystrophy: stiff skin syndrome – a human counterpart of the tight-skin mouse. *J Am Acad Dermatol* 1989;21:943–50.
- McCalmont TH, Gilliam AE. A subcutaneous lattice-like array of thick collagen is a clue to the diagnosis of stiff skin syndrome. *J Clin Pathol* 2012;39:204.
- Haxthausen H. Adiponecrosis e frigore. *Br J Dermatol* 1941;53:83.
- Rotman H. Cold panniculitis in children. *Arch Dermatol* 1966;94:720–1.
- Collins HA, Stahlman M, Scott HW Jr. The occurrence of subcutaneous fat necrosis in an infant following induced hypothermia used as an adjuvant in cardiac surgery. *Ann Surg* 1953;138:880–5.
- Mimouni F, Merlob P, Metzker A, et al. Supraventricular tachycardia: The icebag technique may be harmful in newborn infants. *J Pediatr* 1983;103:337.
- Ter Poorten JC, Hebert AA, Ilkiw R. Cold panniculitis in a neonate. *J Am Acad Dermatol* 1995;33:383–5.
- Epstein EH Jr, Oren ME. Popsicle panniculitis. *N Engl J Med* 1970;282:966–7.
- Lowe IB Jr. Cold panniculitis in children. *Am J Dis Child* 1968;115:709–13.
- Duncan WC, Freeman RG, Heaton CL. Cold panniculitis. *Arch Dermatol* 1966;94:722–4.
- Silverman RA, Newman AJ, LeVine MJ, et al. Poststeroid panniculitis: A case report. *Pediatr Dermatol* 1988;5:92–3.
- Buswell WA. Traumatic fat necrosis of the face in children. *Br J Plast Surg* 1979;32:127–8.
- Moreno A, Marcoral J, Peyri J. Traumatic panniculitis. *Dermatol Clin* 2008;26:481–3.
- Fawcett HA, Smith NP. Injection-site granuloma due to aluminum. *Arch Dermatol* 1984;120:1318–22.
- Chong H, Brady K, Metz D, et al. Persistent nodules at injection sites (aluminum granuloma) – clinicopathologic study. 14 cases with a diverse range of histologic reaction patterns. *Histopathology* 2006;48:182–8.
- Forstrom L, Winkelmann RK. Factitial panniculitis. *Arch Dermatol* 1974;110:747–50.
- Pao W, Duncan KO, Bolognia JL, et al. Numerous eruptive lesions of panniculitis associated with group A *Streptococcus* bacteremia in an immunocompetent child. *Clin Infect Dis* 1998;27:430–3.
- Patterson J, Brown PO, Broecker LR. Infection-induced panniculitis. *J Cutan Pathol* 1989;16:183–93.
- Douvoyiannis M, Litman N, Dulau A, et al. Panniculitis, infection, and dermatomyositis: a case and literature review. *Clin Rheumatol* 2009;28(Suppl.):S57–63.
- Patterson JW, Brown PC, Broecker AH. Infection-induced panniculitis. *J Cutan Pathol* 1989;16:183–93.
- Lassman LP, James CC. Lumbosacral lipomas: critical survey of 26 cases submitted to laminectomy. *J Neurol Neurosurg Psychiatry* 1967;30:174–81.
- Harrist TJ, Gary DL, Kleinman GM, et al. Unusual sacrococcygeal embryologic malformation with cutaneous manifestation. *Arch Dermatol* 1982;118:643–8.
- Goldberg NS, Hebert AA, Esterly NB. Sacral lipomas: The need for neurologic and radiologic evaluation. *Arch Dermatol* 1987;123:711–12.
- Lhowe D, Ehrlich MC, Chapman PH, et al. Congenital intraspinal lipomas: Clinical presentation and response to therapy. *J Pediatr Orthop* 1987;7:531–7.
- Sapp JC, Turner JT, van de Kemp JM, et al. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformation and epidermal nevi (CLOVE syndrome) in 7 patients. *Am J Med Genet A* 2007;143:2944–58.
- Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutation in *PIK3CA* cause CLOVES syndrome. *Am J Hum Genet* 2012;90:1108–15.

62. Romano C, Schepis C. *PTEN* gene: a model for genetic disease in dermatology. *Sci World J* 2012;2012:252457.
63. Buisson P, Ledair MD, Jacquemont S, et al. Cutaneous lipomas in children: 5 cases with Bannayan-Riley-Ruvalcaba syndrome. *J Pediatr Surg* 2006;41:1601-3.
64. Azzoni R, Gerevini S, Cabitza P. Spinal cord sonography in newborns: anatomy and diseases. *J Pediatr Orthop B* 2005;14:185-8.
65. Hughes JA, DeBruyn R, Patel K, et al. Spinal ultrasound in spinal dysraphism. *Clin Radiol* 2003;58:227-33.
66. Park HJ, Park CJ, Yi TY, et al. Nevus lipomatosus cutaneus superficialis. *Int J Dermatol* 1997;36:435-7.
67. Raymond JL, Stoeber P, Amblard P. Nevus lipomatosus cutaneus superficialis, an electron microscopic study of 4 cases. *J Cutan Pathol* 1980;7:295-301.
68. Orteau CH, Hughes JR. Nevus lipomatosus cutaneus superficialis: Overlap with connective tissue naevi [Letter]. *Acta Dermatol Venerol* 1996;76:243-5.
69. Hoffman E, Zurhelle E. [Über einen Naevus lipomatosus cutaneus superficialis der linken Gultaalgegend.] *Arch Dermatol Syphilol* 1921;130:327-33.
70. Jones EW, Marks R, Pongsehirun D. Naevus superficialis lipomatosus. A clinicopathological report of twenty cases. *Br J Dermatol* 1975;93:121-33.
71. Goucha S, Khaled A, Zeglaoui F, et al. Nevus lipomatosus cutaneus superficialis: report of eight cases. *Dermatol Ther (Heidelb)* 2011;1:25-30.
72. Jung S-T, Park H-W, Yun SJ. Giant nevus lipomatosus cutaneus superficialis. *J Am Acad Dermatol* 2012;67:e168-70.
73. Knüttel R, Silver EA. A cerebriform mass on the right buttock. *Dermatol Surg* 2003;29:780-1.
74. Grimalt R, Ermacora E, Mistura L, et al. Encephalocraniocutaneous lipomatosis: Case report and review of the literature. *Pediatr Dermatol* 1993;10:164-8.
75. Haberland C, Perou M. Encephalocraniocutaneous lipomatosis. A new example of ectodermal dysgenesis. *Arch Neurol* 1970;22:144-55.
76. Moog U. Encephalocraniocutaneous lipomatosis. *J Med Genet* 2009;46(11):721-9.
77. Miyao M, Saito T, Yamamoto Y, et al. Encephalocraniocutaneous lipomatosis: A recently described neurocutaneous syndrome. *Childs Brain* 1984;11:280-4.
78. Fishman MA. Encephalocraniocutaneous lipomatosis. *J Child Neurol* 1987;2:186-93.
79. Valera ET, Brosses MS, Scrideli CA, et al. Are patients with encephalocraniocutaneous lipomatosis at increased risk for developing low-grade gliomas? *Childs Nerv Syst* 2012;28(1):19-22.
80. Delfino LN, Fariello G, Quattrocchi CC, et al. Encephalocraniocutaneous lipomatosis (ECCL): neuroradiological findings in three patients and a new association with fibrous dysplasia. *Am J Med Genet A* 2011;155A:1690-6.
81. Rubegni P, Risulo M, Sbrano P, et al. Encephalocraniocutaneous lipomatosis (Haberland syndrome) with bilateral cutaneous and visual involvement. *Clin Exp Dermatol* 2003;28:387-90.
82. Lasiera R, Valencia I, Carapeto FJ, et al. Encephalocraniocutaneous lipomatosis: neurologic manifestations. *J Child Neurol* 2003;18:725-9.
83. Happle R. How many epidermal nevus syndromes exist? *J Am Acad Dermatol* 1991;25:550-6.
84. Ross CM. Generalized folded skin with an underlying lipomatous nevus. *Arch Dermatol* 1969;100:320-3.
85. Schnur RE, Herzberg AJ, Spinner N, et al. Variability in the Michelin tire syndrome, a child with multiple anomalies, smooth muscle hamartoma and familial paracentric inversion of chromosome 7q. *J Am Acad Dermatol* 1993;28:364-70.
86. Sato M, Ishikawa O, Miyachi Y, et al. Michelin tire syndrome: A congenital disorder of elastic fibre formation? *Br J Dermatol* 1997;136:583-6.
87. Kunze J, Riehm H. A new genetic disorder: Autosomal dominant multiple benign ring-shaped skin creases. *Eur J Pediatr* 1982;138:301-13.
88. Gardner EW, Miller HM, Lowney ED. Folded skin associated with underlying nevus lipomatosus. *Arch Dermatol* 1979;115:978-9.
89. Kharfi M, Zarea I, Chaouechi S, et al. Michelin Tire syndrome: a report of 2 siblings. *Pediatr Dermatol* 2005;22:245-9.
90. Eichenfield LF, Cunningham BC, Friedlander SF. Congenital piezogenic-like papules. *Ann Dermatol* 1998;125:182.
91. Larralde de Luna M, Ruiz Leon J, Cabrera HN. [Pedal papules in newborn infants]. [Spanish] *Med Cutan Ibero Lat Am* 1990;18(1):9-12.
92. Larregue M, Varbres P, Echard P, et al. Precalcaneal congenital fibrolipomatous hamartomas (PCFHs). Presented at the Vth International Congress of Pediatric Dermatology, 1996.
93. Warren R, Verbov JL, Ashworth M. Precalcaneal congenital fibrolipomatous hamartoma. *Pediatr Dermatol* 2007;24:74-5.
94. Fangman WL, Prose NS. Precalcaneal congenital fibrolipomatous hamartomas: report of occurrence in half brothers. *Pediatr Dermatol* 2004;21:655-6.
95. Jaffe RH. Recurrent lipomatous tumors of the groin: Liposarcoma and lipoma pseudomyxomatodes. *Arch Pathol* 1926;1:381-7.
96. Van Meurs DP. The transformation of an embryonic lipoma to common lipoma. *Br J Surg* 1947;34:282-4.
97. Chung EF, Enzinger FM. Benign lipoblastomatosis: an analysis of 35 cases. *Cancer* 1973;32:482-92.
98. Mahour GH, Bryan BJ, Isaacs H. Lipoblastoma and lipoblastomatosis - a report of six cases. *Surgery* 1988;104:577-9.
99. Mentzel T, Calonje E, Fletcher CD. Lipoblastoma and lipoblastomatosis: A clinicopathological study of 14 cases. *Histopathology* 1993;23:527-33.
100. Jung SM, Chang DY, Lao CL, et al. Lipoblastoma/lipoblastomatosis: a clinicopathologic study of 16 cases in Taiwan. *Pediatr Surg Int* 2005;21:809-12.
101. Dutton J, Escaravage GK, Fowler A, et al. Lipomatosis: case report and review of the literature. *Ophthalm Plast Reconstr Surg* 2011;27:417-21.
102. Brandal P, Bjerkehagen B, Heim J. Rearrangement of chromosome region 8q 11-13 in lipomatous tumours: correlation with lipomatous morphology. *J Pathol* 2006;208:388-94.
103. Gaffney EF, Vellios F, Hargreaves HK, et al. Lipoblastomatosis: ultrastructure of two cases and relationship to human fetal white adipose tissue. *Pediatr Pathol* 1986;5:207-16.
104. Chen CW, Chang WC, Lee HS, et al. MRI features of lipoblastoma: differentiating from other palpable lipomatous tumor in pediatric patients. *Clin Imaging* 2010;34:453-7.
105. Donohue WL, Uchida IA. Leprechaunism: a euphemism for a rare familial disorder. *J Pediatr* 1954;45:505-19.
106. Donohue WL. Dysendocrinism. *J Pediatr* 1948;32:739-48.
107. Musso C, Cochran E, Moran SA, et al. Clinical course of genetic diseases of insulin receptor (type A and Rabson-Mendenhall syndromes): a 30-year prospective. *Medicine (Baltimore)* 2004;83:209-22.
108. Taylor SI. Lilly lecture: Molecular mechanism of insulin resistance. *Diabetes* 1992;41:1473-90.
109. Elsas LJ, Endo F, Strumlauf E, et al. Leprechaunism: An inherited defect in high-affinity insulin receptor. *Am J Human Genet* 1985;37:73-88.
110. Kostolanyi F. Leprechaunism/Donohue syndrome/insulin receptor gene mutations: A syndrome delineation story from clinicopathological description to molecular understanding. *Eur J Pediatr* 1997;156:253-5.
111. Ozbey H, Ozbey N, Tunnessen W. Picture of the month: Leprechaunism. *Arch Pediatr Adolesc Med* 1998;152:1031-2.
112. Kadowaki T, Bevins CL, Cama A. Two mutant alleles of the insulin receptor gene in a patient with extreme insulin resistance. *Science* 1998;240:787-90.
113. de Bock M, Hayes I, Semple R. 'Donohue syndrome.' *J Clin Endocrinol Metab* 2012;97:1416-17.
114. Semple RK, Savage DB, Cochran EK, et al. Genetic syndromes of severe insulin resistance. *Endocr Rev* 2011;32:498-514.
115. Semple RK, Williams RM, Dunger DB. What is the best management strategy for patients with severe insulin resistance. *Clin Endocrinol* 2010;73:286-90.
116. Berardinelli W. An undiagnosed endocrinometabolic syndrome: Report of 2 cases. *J Clin Endocrinol* 1954;14:193-204.
117. Seip M. Lipodystrophy and gigantism with associated endocrine manifestations: A new diencephalic syndrome? *Acta Pediatr Scand* 1959;48:555-74.
118. Hershman O. Generalized lipodystrophy, congenital and acquired (lipoatrophy). *Acta Pediatr* 1996;413:2-28.
119. Garg A. Lipodystrophies: Genetic and acquired body fat disorders. *J Clin Endocrinol Metab* 2011;96:3313-25.
120. Subauste AR, Das AK, Li X, et al. Alterations in lipid signaling underlie lipodystrophy secondary to AGPAT2 mutations. *Diabetes* 2012;61(11):2922-31.
121. Arboleda G, Morales LC, Quintero H, et al. Neonatal progeroid syndrome (Wiedemann-Rautenstrauch syndrome): report of three affected sibs. *Am J Med Genet A* 2011;155A:1712-15.
122. Jaeken J, Stibler H, Hagberg B. The carbohydrate-deficient glycoprotein syndrome. *Acta Paediatr Scand* 1991;375:S5-71.

123. Krasnewich D, Gahl WA. Carbohydrate-deficient glycoprotein syndrome. *Adv Pediatr* 1997;44:109–39.
124. Collins AE, Ferriero DM. The expanding spectrum of congenital disorders of glycosylation. *J Pediatr* 2005;147:728–30.
125. Woods AG, Woods CW, Snow TM. Congenital disorders of glycosylation. *Adv Neonatal Care* 2012;12:90–5.
126. Jaeken J, Vanderschueren-Lodewyckx M, Casaer P. Familial psychomotor retardation with markedly fluctuating serum prolactin, FSH and GH levels, partial TBG deficiency, increased CSF protein: a new syndrome? *Pediatr Res* 1980;14:129.
127. Charlwood J, Clayton P, Keir G, et al. Prenatal diagnosis of the carbohydrate-deficient glycoprotein syndrome type 1A (CDG1A) by a combination of enzymology and genetic linkage analysis after amniocentesis or chorionic villus sampling. *Prenat Diagn* 1998;18:693–9.
128. Rutledge P. Gangliosidoses and related lipid storage diseases. In: Rimoin DL, Connor JM, Pyeritz RE, editors. *Emery and Rimoin's principles and practice of medical genetics*. 3rd ed. New York: Churchill Livingstone; 1996. p. 2113–14.

Introduction

Skin disorders characterized by infiltrative lesions can be present at birth or develop during the first few months of life. Some represent frank neoplasms, both benign and malignant, whereas others are the result of metabolic errors. In most instances, diagnosis is facilitated by skin biopsy, in which certain cell types can be identified by special stains and immunologic markers. Others require special enzyme assays for definitive diagnosis.¹

Neoplastic disorders

LEUKEMIA

Congenital leukemia is a rare hematologic disorder. Less than 1% of all childhood leukemia is diagnosed in newborns.² The majority of neonates have acute myeloid leukemia (AML), while acute lymphoblastic leukemia (ALL) is less common. The most frequently occurring chromosomal abnormality in both congenital AML and ALL is a translocation involving the mixed lineage leukemia (MLL) gene. To differentiate congenital leukemia from the several infectious and proliferative disorders that can easily mimic this condition, the following diagnostic criteria are employed:

1. The presence of immature white cells in the blood
2. Infiltration of these cells into extrahematopoietic tissues
3. The absence of diseases that can cause leukemoid reactions (such as erythroblastosis fetalis and a variety of congenital infections)
4. The absence of chromosomal disorders that are associated with 'unstable' hematopoiesis (such as trisomy 21).^{3,4}

Cutaneous findings

The cutaneous manifestations of congenital leukemia consist of petechiae, ecchymoses, and skin nodules. Leukemia cutis is seen in approximately 60% of patients with congenital leukemia. The firm nodules are usually 1–2.5 cm in diameter and blue to purple in color (Fig. 28.1). They are often widely spread over the skin surface, although congenital leukemia may present as a single nodular cutaneous lesion.⁵ Diffuse calcinosis cutis in an infant with congenital AML has been reported.⁶ Congenital AML may be manifested by 'blueberry muffin' lesions,⁷ and Darier's sign has been observed.⁸ The clinical signs and symptoms include hepatosplenomegaly, pallor, lethargy, and respiratory distress. Lymphadenopathy occurs in some infants.

Diagnosis

Biopsy of a cutaneous lesion reveals a dense pleomorphic mononuclear cell infiltrate in the dermis and subcutaneous fat. Atypical mitotic figures may be present. The diagnosis of congenital leukemia can usually be confirmed by a complete blood count, bone marrow aspirate, and radiographs of the skull and

long bones. In every case, cytogenetic studies must be performed to exclude the possibility of transient myeloproliferative disorder, which is usually associated with trisomy 21.⁹ This disorder is also associated with a diffuse vesiculopustular eruption (see Chapter 10).^{10,11}

Treatment and course

Congenital leukemia is often fatal, with overall survival ranging from 10–25%.⁵ Treatment consists of intensive multiagent chemotherapy. The benefit of hematopoietic stem cell transplantation remains uncertain. Spontaneous remission of congenital leukemia cutis, usually without involvement of blood or bone marrow, has been reported.^{12–14}

LEUKEMIA IN INFANCY

Leukemia occurring in infants under the age of 1 year bears many similarities to congenital and neonatal forms. Patients in this age group also have a high incidence of MLL rearrangements. Typical lesions include violaceous macules, nodules, and plaques. Patients with AML may present with larger purplish tumors, while those with ALL may develop numerous prurigo-like papules. The development of granulocytic sarcoma (formerly known as chloroma) in the periorbital skin of infants has also been reported.¹⁵

LANGERHANS' CELL HISTIOCYTOSIS

Langerhans' cell histiocytosis (LCH), a rare proliferative disorder, may be present at birth or may develop during the first few months of life. The estimated incidence of neonatal LCH is 9/1 000 000 in infants <1 year of age, with disease presentation during the first month of life in about 6% of those affected.^{16,17} The spectrum of clinical presentations, and the clinical course, is extremely varied and ranges from the simple presence of one or several nodules, widespread crusted papules and vesicles, to severe, progressive multisystem disease.

Cutaneous findings

The most frequent cutaneous presentation – particularly in infants and newborns – consists of multiple widespread vesiculopustules with umbilication and a hemorrhagic crust.^{18–23} Lesions tend to favor the scalp, trunk, diaper area, and skin folds (Fig. 28.2A). They may begin as subtle brown or pink papules, and evolve into crusted or purpuric lesions (Fig. 28.2B). Papular lesions may coalesce into areas of superficial ulceration with oozing, especially in intertriginous areas. Characteristic lesions also include fissures behind the ears, and crusting and oozing of the external ear canals. The scalp is a frequent site of involvement, and the coalescence of crusted and scaling lesions may lead to partial alopecia. Presentation as a 'blueberry muffin



Figure 28.1 (A) The large nodule above the eye of this neonate represented a manifestation of congenital leukemia resulting from acute lymphocytic leukemia. (B) Congenital acute myelogenous leukemia with purpuric nodules and areas of macular purpura.



Figure 28.2 (A) Multiple pustules and erosions are evident in this young infant with Langerhans' cell histiocytosis and multisystem involvement. (B) Extensive LCH with purpuric and crusted papules.

baby,' with cutaneous hematopoiesis, has been reported.²⁴ Nodules and petechiae, which may involve the palms and soles, are also observed. Oral lesions are relatively common, and can develop before skin lesions. They may appear as superficial ulcerations or erosions, but these are often associated with underlying alveolar bone disease. Other oral manifestations include gingival bleeding, facial swelling, and pain. Premature eruption and loss of teeth, and destruction of alveolar bone are characteristic. Involvement of the vulva and vagina may also occur. Nail involvement consists of subungual pustules, paronychia, onycholysis, and longitudinal grooving. Permanent nail dystrophy may result.²⁵

CONGENITAL 'SELF-HEALING' LANGERHANS' CELL HISTIOCYTOSIS

A multifocal congenital form of LCH, which has sometimes been called 'Hashimoto–Pritzker disease'²⁶ is characterized by papulonodular and papulovesicular skin lesions. Cases presenting with a solitary nodule have also been reported. These solitary skin nodules are usually red-brown and often have a

hemorrhagic quality, ulceration, or crusting.²⁷ Most affected infants have lesions at the time of birth without evidence of other organ system involvement (Figs 28.3, 28.4).²⁶ Skin lesions typically resolve spontaneously, without sequelae but localized areas of scar or atrophy can occur.^{28–30} However, skin relapse, bone disease, late-onset diabetes insipidus, and even progression to severe LCH has been reported in children who present with congenital skin lesions.³¹

Extracutaneous findings

The majority of infants with all forms of congenital or neonatal Langerhans' cell histiocytosis will show evidence of multisystem disease.^{31–33} Bone lesions are the most frequent noncutaneous manifestation. Findings may include asymptomatic lytic lesions, deformation, fracture, or medullary compression. The skull is a common site, and disease in that location manifests on X-ray as punched-out lesions in the cranial vault. Mastoid involvement may lead to mastoid necrosis, and destruction of the ossicles may result in deafness. Intracranial disease may cause exophthalmos and diabetes insipidus. Lymph node involvement is seen in a significant percentage of patients, and tends to occur



Figure 28.3 Multiple crusted papules are typical of the 'self-healing' variant of congenital Langerhans' cell histiocytosis.



Figure 28.4 A congenital nodule in the inguinal area was found on biopsy to be congenital Langerhans' cell histiocytosis. It resolved without further sequelae.

in the cervical chain. Pulmonary disease may be associated with cough and tachypnea. Other findings include bullae formation and diffuse interstitial fibrosis. Invasion of the liver may cause mild cholestasis, but eventually evolve to sclerosing cholangitis. Severe fibrosis of the liver results in ascites, jaundice, and liver failure. Involvement of the spleen may worsen the severity of

thrombocytopenia. Gastrointestinal disease is reported to occur in a small percentage of patients.³⁴ Characteristic findings are vomiting, diarrhea, protein-losing enteropathy, and failure to thrive secondary to malabsorption. The most common endocrine manifestation is diabetes insipidus. This occurs most often in children with extensive disease and involvement of the skull. Langerhans' cells may also infiltrate the thyroid and pancreas.

Diagnosis

Biopsy of a cutaneous lesion reveals a diffuse infiltration of histiocytes with abundant eosinophilic cytoplasm and eccentric, indented nuclei. In some cases, the nuclei may appear pleomorphic or atypical. Positive CD1a and/or CD207 (Langerin) staining of the lesional cells is needed for a definitive diagnosis. Electron microscopy is no longer required since it is now known that the expression of Langerin correlates with the ultrastructural presence of Birbeck granules.³⁵

Preliminary laboratory evaluation of the patient with biopsy-proven skin lesions must include a complete blood count (CBC), serum electrolytes, urine specific gravity, and assessment of liver function. Examination of the bone marrow may show the presence of increased histiocytes. Skeletal survey, chest radiographs, and magnetic resonance imaging (MRI) may be used to determine the extent of bone, pulmonary, liver, spleen, and CNS involvement.

Differential diagnosis

The pustular and intertriginous lesions of LCH in neonates and infants may be confused with candidiasis, seborrheic dermatitis, psoriasis and scabies. Congenital LCH must also be differentiated from other neoplastic disorders, such as leukemia and lymphoma; from congenital infections, especially herpes simplex; and from those viral disorders associated with 'blueberry muffin' lesions.

Treatment and course

The majority of children with infantile LCH develop multisystem disease. The prognosis seems to be better in congenital 'self-healing' LCH, but multisystem disease is still possible, and such neonates must be followed to assure that they do not develop extracutaneous disease later on. Survival of infantile LCH in the past few decades has improved from 57% to 74%.^{16,35} Single-system disease has a significantly higher rate of survival (94%), but patients with initial liver involvement have a much poorer prognosis, with a 25% 5-year survival. In children with LCH limited to the skin (<5% of cases), a 'wait and see' approach should be accompanied by careful monitoring for disease progression. Children in this category may benefit from therapy with mild to moderate-strength topical corticosteroids. Children with multisystem disease are treated with chemotherapy; standard treatment is based on steroids and vinblastine.

LYMPHOMA

Mycosis fungoides

Mycosis fungoides is extremely rare in young children, but a number of cases have been well documented.³⁶ The patients presented with widespread and persistent scaly plaques. Several cases were initially misdiagnosed as either atopic dermatitis or tinea corporis, leading to a significant delay in diagnosis.

Primary cutaneous anaplastic large cell lymphoma

This form of cutaneous T-cell lymphoma is characterized by large tumor cells that express CD30 antigen. Clinical presentations consists of papules, and plaques which may ulcerate. The rare occurrence of this disease during the first 2 years of life has been documented.³⁷

Lymphomatoid papulosis

Lymphomatoid papulosis is a chronic, recurrent disorder characterized by the presence of reddish brown papules and nodules. Progression to malignant forms of lymphoma is rarely reported. In one series of pediatric patients, including children under the age of 2 years, a benign course, accompanied by a predominance of CD8+ lymphocytes was observed.³⁸

Cutaneous B-cell lymphoma

Primary cutaneous B-cell lymphoma is extremely rare in infancy. Primary cutaneous lymphoblastic lymphoma, presenting with firm violaceous nodules with overlying telangiectasia, has been reported to occur in some children under the age of 2 years.^{39,40} Subcutaneous panniculitis-like T-cell lymphoma, with purplish tender nodules in an acral distribution, has also been reported to occur in infancy.^{41,42}

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition characterized by hepatosplenomegaly, cytopenias and prolonged fever.⁴³ Central nervous system (CNS) symptoms are frequent. Some children have been noted to have an evanescent macular and papular skin eruption, sometimes associated with episodes of fever (Fig. 28.5). Genetic HLH occurs in familial forms (FHLH), and in association with



Figure 28.5 Familial hemophagocytic lymphohistiocytosis with erythematous macules and abdominal distension.

a variety of immune deficiencies.⁴⁴ Acquired and genetic forms may both be triggered by infections.

Diagnosis is made by the detection of a non-malignant mixed lymphohistiocytic proliferation in the reticuloendothelial system, with evidence of hemophagocytosis. Without treatment, FLH is usually rapidly fatal. The immediate goal of treatment is suppression of the increased inflammatory response by immunosuppressive/immunomodulatory agents and cytotoxic drugs. Genetic cases can only be cured with stem cell transplantation.⁴⁵

INFANTILE FIBROSARCOMA

Congenital/infantile fibrosarcoma is a rare tumor that occurs most frequently on the extremities. Lesions are seen less commonly on the head, neck, and trunk, and may also occur in the retroperitoneum.⁴⁶ The tumor may be present at birth, or may develop during early infancy.

Cutaneous findings

Fibrosarcoma most often presents as a soft tissue mass, sometimes with rapid growth. The overlying skin may be tense, shiny, and erythematous, and ulceration may occur (Fig. 28.6).⁴⁷

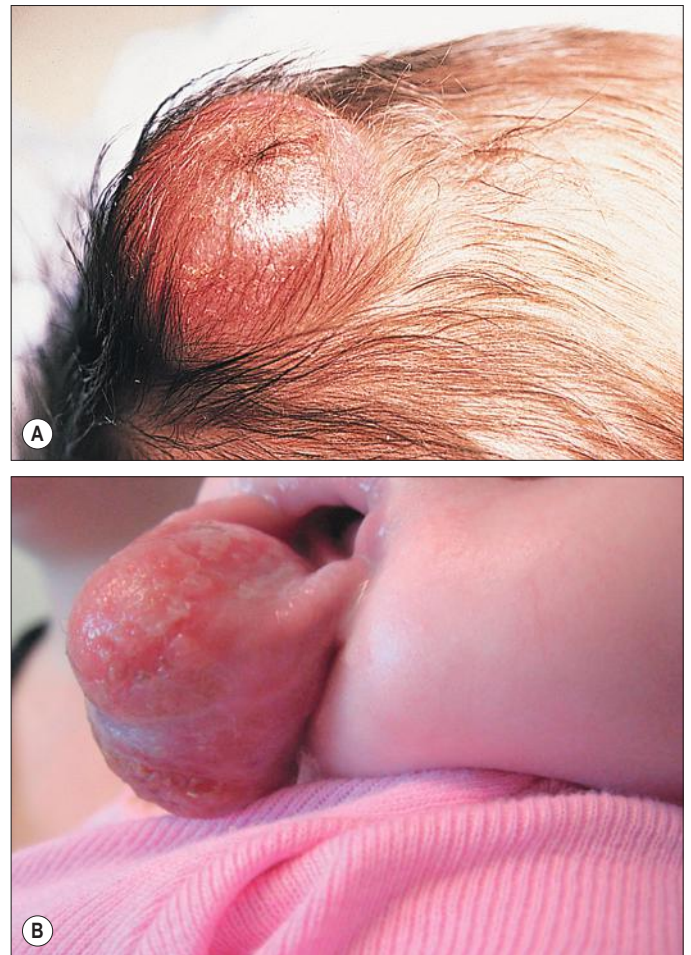


Figure 28.6 (A) Infantile fibrosarcoma of the scalp in a 15-day-old boy. (B) Fibrosarcoma of the lip of a 7-week-old infant. This tumor was present at birth but grew rapidly in the first few weeks of life. It was initially misdiagnosed and treated as an infantile hemangioma. (Courtesy of Linda Beets-Shay, MD.)

Diagnosis

MRI is useful in defining the extent of the lesion, but the diagnosis is largely based on histology. Histologic examination reveals a highly cellular fibroblastic proliferation, with sizeable vascular clefts and occasional myxoid degeneration and hemorrhagic necrosis.⁴⁸ Analysis of the biopsy sample for the recurrent translocation t(12;15)(p13;q25) is highly recommended.⁴⁹

Differential diagnosis

Clinically, infantile fibrosarcomas are easily confused with either hemangiomas or vascular/lymphatic malformations.^{50,51} Transient consumptive coagulopathy mimicking Kasabach–Merritt phenomenon has been reported, causing confusion with other vascular tumors (see [Chapters 21](#) and [22](#)).⁵² The differential diagnosis also includes rhabdomyosarcoma and infantile myofibromatosis.

Treatment and course

The risk of metastasis, especially in cutaneous lesions, is considerably lower in infants (approx. 8%) than in older patients.⁵³ Treatment consists of wide local excision. Chemotherapy has been used in some patients to reduce the lesion mass preoperatively so as to avoid the need for mutilating surgery, and for lesions that are not resectable.⁵⁴ Close follow-up to monitor for the presence of local recurrence and metastatic disease, is mandatory.⁵⁵

DERMATOFIBROSARCOMA PROTUBERANS

Dermatofibrosarcoma protuberans (DFSP) is a fibrohistiocytic tumor with low metastatic potential and a high incidence of local recurrence. Congenital DFSP is rare, but a number of cases have been reported.^{56–58} Another neoplastic disorder, giant cell fibroblastoma, can also present in early infancy ([Fig. 28.7](#)). Some authors consider this to be a variant of DFSP; others consider it to be a separate entity, but believe that hybrids of giant cell fibroblastoma and DFSP may sometimes occur.



Figure 28.7 Giant cell fibroblastoma, considered by some to be a variant of dermatofibrosarcoma protuberans.

Cutaneous findings

Characteristically, DFSP begins as an atrophic plaque surrounded by an area of bluish discoloration. Over time, as the cellular proliferation extends into the deep dermis and subcutaneous tissues, nodules develop on the plaque surface ([Fig. 28.8](#)). Similar to the lesions seen in older patients, congenital DFSP occurs most commonly on the trunk and proximal extremities.⁵⁹ Giant cell fibroblastoma more typically presents during infancy as a slow-growing soft-tissue mass.

Diagnosis

Histologically, DFSP is characterized by the presence of spindle cells in a well-defined and uniform storiform pattern. Focal myxoid change and scarring may occur. Tumor cells express vimentin, but are negative for S100 protein, epithelial membrane antigen, and smooth muscle actin.⁶⁰ Diagnosis can be facilitated by detection of the collagen type I α 1/platelet-derived growth factor β -chain fusion gene by means of reverse transcriptase–polymerase chain reaction or fluorescence in situ hybridization.⁵⁸

Differential diagnosis

Clinically, the differential diagnosis of congenital DFSP includes fibrous hamartoma of infancy, infantile myofibromatosis, lipoblastoma (see [Chapter 27](#)), and vascular tumors and malformations. Neurofibroma and fibrous histiocytoma may mimic DFSP histologically.

Treatment

Because of the high risk of recurrence, adequate surgical margins must be obtained. Mohs micrographic surgery is the preferred approach in older children. However, in young infants, this can be difficult to arrange logistically in a child requiring general anesthesia for the excision, so wide excision is generally performed.⁶¹

NEUROBLASTOMA

Cutaneous findings

Neuroblastoma is among the most common solid tumors of early childhood, and may present at birth or in early infancy.⁶² In stage 4, neuroblastoma cutaneous metastases present as



Figure 28.8 Nodular, plaque-type dermatofibrosarcoma protuberans.



Figure 28.9 Congenital neuroblastoma: blue nodules on the face. (Courtesy of Dr Bari Cunningham.)

bluish, firm papules and nodules on the trunk and extremities (Fig. 28.9). Several authors have reported that these lesions may blanch after palpation, and that the blanching persists for 30–60 min.^{63,64} This phenomenon has been related to the localized release of catecholamines. Periorbital ecchymoses, secondary to orbital metastases, may also occur.

Extracutaneous findings

Metastatic disease, characterized by fever, hepatomegaly, and failure to thrive, is often present at the time of diagnosis. The primary lesion is usually located in the upper abdomen, arising within the adrenal gland, and may be detected as an enlarging mass.

Diagnosis

Diagnosis of the cutaneous lesions is based on histologic examination. The dermal or subcutaneous infiltrate consists of small cells with scanty cytoplasm and heterochromatic nuclei. Pseudorosettes and mature ganglion cells are present in differentiated lesions. Immunoperoxidase staining may establish the presence of neuron-specific proteins.

Although most cases of neuroblastoma are sporadic, autosomal dominant inheritance may occur. Concordance in monozygotic twins has also been reported.⁶⁵ The location and extent of the primary lesion is most often established by computed tomography (CT) or MRI. Increased urinary catecholamines are present in the majority of patients.

Differential diagnosis

Clinically and histologically, the lesions of neuroblastoma must be differentiated from leukemia and lymphoma. In addition, the blueberry muffin appearance of some lesions may mimic congenital rubella or cytomegalovirus infection.

Treatment and course

The prognosis of neuroblastoma depends on the age of the patient and the extent of the disease (stages 1–4S). The survival rate at 2 years in children who are diagnosed under the age of 1 year exceeds 80%. In some patients, especially with stage 4S, spontaneous differentiation to neural ganglion cells and

regression without treatment have been reported. The choice of treatment depends on staging and patient age, and consists of various combinations of surgery, radiation therapy, and chemotherapy.⁶⁶

RHABDOMYOSARCOMA

Rhabdomyosarcoma (RMS) presents most commonly as a tumor of the head and neck (Fig. 28.10A,B). There are two histologic subtypes: embryonal RMS, which is more common and usually has a better prognosis, and alveolar RMS, which is characterized by the $t(2;13)(q35;q14)$ and $t(1;13)(p36;q14)$ chromosomal translocations.⁶⁷ An association between RMS and both neurofibromatosis type 1 and major congenital abnormalities has been observed.⁶⁸ RMS arising in children with giant congenital melanocytic nevi has also been reported.⁶⁹ A cutaneous origin of RMS is rare. Most often, extension of the tumor into the dermis results in the evolution of a nodule or plaque.⁷⁰ Facial lesions are most common and these must be differentiated clinically from dermoid cysts, hemangiomas, and inflammatory disorders. Histologically, there is a dermal infiltrate of small blue cells with occasional differentiation toward rhabdomyoblasts. The presence of staining for desmin, vimentin and muscle actin help to differentiate these lesions from neuroblastoma and lymphoma.⁷¹

Treatment is based on the extent of local, regional, and distant disease, and consists of a combination of surgery, radiation, and chemotherapy. Combined modality therapy results in a long-term survival of >50%.⁷²

RHABDOID TUMOR

Rhabdoid tumor is a rare and highly malignant neoplasm with rapid growth and early metastases. The skin may be the site of a primary tumor or of metastases from other locations (Fig. 28.10C). The majority of neonates are found to have metastatic disease at the time of diagnosis, and brain tumors are a frequent finding. Characteristic bluish cutaneous nodules may be located over the entire skin surface. The tissue of rhabdoid tumors has a characteristic genetic alteration in the region 11.2 of the long arm of chromosome 22 (22q11.2), characterized by the deletion or mutation of the *hSNF5/SMARCB1/INI1* gene resulting in the loss or reduced expression of INI protein. The survival rate is extremely low.^{49,71}

MALIGNANT MELANOMA

Malignant melanoma is very rare in neonates and infants but can develop in several different clinical situations^{73–75}:

1. Congenital malignant melanoma arising *de novo*. Malignant melanoma may present at birth as a nodular, darkly pigmented, rapidly growing skin lesion sometimes with ulceration.^{76,77} In these neonates, there is no clinical or histologic evidence of an underlying congenital melanocytic nevus, and there is no maternal history of melanoma (Fig. 28.11).
2. Congenital malignant melanoma arising in a giant congenital melanocytic nevus. In these patients, ulcerated and nonulcerated nodules may be present in the congenital melanocytic nevus and on adjoining skin. The presence of prenatal metastatic disease has been noted to occur in some children.^{78,79}



Figure 28.10 (A) Rhabdomyosarcoma. A firm, vascular-appearing tumor of the hand. (B) Alveolar rhabdomyosarcoma on the forehead of a 6-day-old infant with multifocal disease at birth. (C) Rhabdoid tumors. Multiple firm subcutaneous nodules were present at birth along with hepatosplenomegaly and other internal sites of involvement. The prognosis of this presentation is extremely poor.

3. Congenital malignant melanoma arising from leptomeningeal melanocytosis. Children with leptomeningeal melanocytosis may have a high lifetime incidence of metastatic malignant melanoma. Rarely, these metastatic cutaneous lesions may be present at birth.
4. Congenital malignant melanoma secondary to maternal melanoma. Transplacental transmission from a mother



Figure 28.11 Congenital malignant melanoma, arising de novo on normal skin.

with metastatic disease may occur.⁸⁰ Typically, the skin lesions are multiple pigmented macules, papules, and nodules, and there may be multiorgan involvement.

5. Spitzoid melanoma is a relatively rare subtype which shares histopathologic features with Spitz nevus.⁸¹ The prognosis is variable; Spitzoid melanoma with regional lymph node involvement and no further progression has been reported.⁸² However, some cases have resulted in a fatal outcome.

The diagnosis of malignant melanoma is made by excisional biopsy of the suspicious lesion, and the cellular and architectural features are similar to those seen in melanoma in older patients. However, a wide variety of benign and malignant tumors, with small round cell, spindled, neural, and epithelioid components, have been observed within congenital melanocytic nevi.⁷⁷ In addition, histologic changes within a benign, congenital melanocytic nevus may include displaced large melanocytes within the epidermis, and heterogeneous patterns of melanocytic hyperplasia.⁷⁸ In some cases, findings of this type have led to an incorrect diagnosis of malignant melanoma. Biopsies of congenital melanocytic nevi, especially in the neonate, must therefore be interpreted with caution.^{73,83,84}

The evaluation of children with all forms of melanoma must include a complete evaluation for local and distant lymph node involvement. Metastases are most frequently seen in the CNS, bones, lungs, and liver.

Treatment is based on lesion thickness and the stage of the disease. Therapeutic options include lymph node dissection of enlarged draining regional nodes and chemotherapy for metastatic disease.⁷⁹ Lesions arising de novo have an unpredictable prognosis, and long-term survival has been reported in children who developed both local recurrences and metastatic lesions. Melanomas arising in congenital melanocytic nevi appear to have a significantly worse prognosis. Congenital malignant melanoma secondary to maternal melanoma is usually fatal, but spontaneous regression has been reported to occur.⁸⁰

CONGENITAL TERATOMA

Congenital teratomas most frequently present as masses in the cervical, nasopharynx, or sacrococcygeal region.⁸⁵ These are

usually benign tumors, which are derived from elements of all three germinal layers, and which result in significant morbidity and mortality because of their location, size, and tendency to cause airway obstruction. Approximately 10–20% of SCT may contain primitive germ cell tumor components, and can evolve to actual malignancy. This risk increases significantly with age at diagnosis. The diagnosis requires complete pathologic examination of the entire resected tumor for malignant change. The differential diagnosis includes dermoids and lymphatic or vascular birthmarks. Treatment consists of complete surgical excision.⁸⁶

Infiltrative disorders

MASTOCYTOSIS

Mastocytosis refers to a disease spectrum with varied presentations, all characterized by infiltration of benign mast cells (MC) in the skin or other organs. ‘Mastocytosis in the skin’ or MIS is the designation given to patients who have cutaneous MC lesions and have not been evaluated for systemic involvement (e.g., bone marrow examination), typically the case in children. A total of 55% of cases develop during the first 2 years, and an additional 10% develop before puberty.⁸⁷ Cases developing after puberty are classified as adult onset. Both sexes are affected equally. MIS is subclassified into maculopapular cutaneous mastocytosis (MPCM, also known as urticaria pigmentosa, UP), solitary mastocytoma, and diffuse cutaneous mastocytosis (DCM). However, many display overlapping features. MPCM is the most common clinical manifestation of mastocytosis. Solitary mastocytoma is less common, although it may be underreported, and DCM, the most severe form, is rare. Most cases are sporadic; however, there are several reports of MPCM affecting multiple family members, and some believe DCM can be inherited in an autosomal dominant fashion.^{87–89} Telangiectasia macularis eruptiva perstans (TMEP) has been reported rarely in the neonatal period, with onset typically during adulthood.

Cutaneous findings

Most patients with MIS exhibit Darier’s sign, which is the development of an urticarial wheal and flare after firm stroking of lesional skin. This cutaneous finding represents the response to physical disruption of the granular contents of mast cells, particularly histamine. Rarely, flushing and hypotension have resulted from stroking of a large lesion or from surgery. Some patients display dermatographism, the formation of linear urticarial plaques following scratching of uninvolved skin. However, this nonspecific finding also occurs in up to 5% of the general population. A variety of physical stimulants and drugs can evoke mast cell degranulation, resulting in urtication, bulla formation, or systemic manifestations (flushing, hypotension, or shock) (Box 28.1).

Pruritis is typical, although many patients have no symptoms. It may be periodic or unremitting. Excoriations may be observed. In children less than 2 years old, vesicles and bullae can develop, and may be observed in all forms of cutaneous mastocytosis except telangiectasia macularis eruptiva perstans. The tendency to blister diminishes over 1–3 years. In one series, generalized flushing was observed in 65% of patients with all forms of the disease.⁹¹

BOX 28.1 HISTAMINE-RELEASING TRIGGERS TO AVOID IN MASTOCYTOSIS

DRUGS

- Narcotics (opiates): codeine, meperidine, morphine, dextromethorphan, etc.
- Aspirin (acetylsalicylic acid) and related analgesics
- Alcohol
- Polymyxin B
- D-tubocurarine^a
- Iodine-containing radiologic contrast dyes
- Cholinergic medications (scopolamine, etc.)
- Thiamine

PHYSICAL STIMULI

- Pressure or friction
- Temperature changes (especially bathing)
- Sunlight or intense UV exposure

OTHER

- Venoms (IgE-mediated hymenoptera venom)
- Polymers (dextran)
- Biological peptides (substance P, somatostatin)

^aGeneral anesthesia is not contraindicated but should be approached cautiously; lorazepam has been shown to be safe for routine sedation in infants.⁹⁰



Figure 28.12 Solitary mastocytoma on the leg of a young infant with a centrally urticated plaque with surrounding flare, demonstrating a positive Darier’s sign.

SOLITARY MASTOCYTOMA

Solitary mastocytoma most often appears in the first 3 months of life. It presents as one isolated, skin-colored to light brown, 1–5 cm, oval to round macule or slightly elevated papule, nodule or plaque (Fig. 28.12). In patients with limited lesions, typically 1–3, the term solitary mastocytoma may be used. Some lesions have a pink or yellow hue. Any cutaneous surface may be affected, but the trunk, upper extremities, and neck are favored locations. Most new lesions appear within 2 months of the initial lesion, more can develop over time and individual lesions may enlarge for several months.

MACULOPAPULAR CUTANEOUS MASTOCYTOSIS (MPCM)/URTICARIA PIGMENTOSA

MPCM, or urticaria pigmentosa, generally develops between 3 and 9 months of life. The lesions appear as multiple, fixed, tan-brown, hyperpigmented macules and papules which can become widespread but usually are discrete and scattered. In rare cases, nodules or skin lesions coalescing into plaques with increased skin markings may develop (Fig. 28.13). Early lesions of MPCM may mimic recurrent urticaria until pigmentation becomes apparent. Any cutaneous surface may be affected, including mucous membranes, but most are on the trunk. Additional lesions of MPCM may develop for several months after the initial diagnosis is made.

DIFFUSE CUTANEOUS MASTOCYTOSIS

Diffuse cutaneous mastocytosis (DCM) is characterized by widespread infiltration of mast cells throughout the skin (Figs 28.10–28.12, 28.14). It presents in the first 3 years of life, and is characterized by normal-appearing, or generalized thickening and palpable edema of the skin, with or without the presence of typical MPCM lesions. The skin may be normal in color or display a reddish-yellow hue. The first sign of DCM is most often serous and hemorrhagic bullae with secondary erosions, sometimes following minor trauma. Severe dermatographism with resultant bullae and flushing may also occur.

TELANGIECTASIA MACULARIS ERUPTIVA PERSTANS (TMEP)

Infantile TMEP presents with congenital or acquired asymptomatic, 1–4 cm, sharply defined, round or oval, telangiectatic,

red-brown patches that resemble small capillary malformations. The patches blanch with pressure, but Darier's sign is reportedly negative. The few documented cases have remained stable over time, and multiple family members can be affected.⁹²

Extracutaneous findings in mast cell disease

Most infants with MIS do not have evidence of extracutaneous disease, but the risk increases with extent of cutaneous disease or symptoms such as flushing or recurrent diarrhea. Outside of the skin, the bone marrow is most often affected. Mast cell hyperplasia in lymph nodes, spleen, liver, bone or GI tract occurs rarely.⁹³ Associated symptoms in infants is variable and commensurate with local or systemic MC-mediator release or organ dysfunction from MC infiltration of organs. Signs and symptoms include diarrhea, vomiting, abdominal pain, bone pain, headache, hypotension, and shock. Prolonged bleeding in the skin and GI tract may occur, and is more frequent in infants with DCM. In these children, heparin from mast cells acts as a local anticoagulant. Elevated levels of circulating histamine, which stimulates gastric acid secretion, may result in gastric ulceration and gastrointestinal hemorrhage.⁹⁴ Children with DCM have the highest incidence of visceral mast cell disease and associated systemic manifestations. MPCM in infants is rarely associated with visceral involvement, and visceral involvement does not appear to occur in children with solitary mastocytomas. The incidence of allergic disease is not increased in children with mastocytosis, but the severity of allergic reactions is increased and the risk of anaphylactoid reactions (e.g., to hymenoptera stings) is also increased.

Serum tryptase level is the best screening test for extracutaneous disease in the setting of extensive cutaneous disease or signs or symptoms of more widespread disease. If serum tryptase is persistently elevated (i.e., >20 ng/ml with normal being ~5 ng/ml) and systemic mastocytosis is clinically suspected,



Figure 28.13 Multiple lesions of urticaria pigmentosa in a 1-month-old infant.



Figure 28.14 Focal blister formation in an infant with diffuse cutaneous mastocytosis.

bone marrow evaluation should be considered.⁹⁵ The optimal cutoff for baseline serum tryptase levels in children with MIS that predict the need for daily anti-mediator therapy, hospitalization, and ICU management is 15.5 ng/ml, and 30.8 ng/ml respectively (for sensitivity and specificity of 100% and 95%, and 100% and 96%, respectively).^{96,97}

Etiology and pathogenesis

The cause of mastocytosis is unknown. However, activating mutations in the *c-kit* proto-oncogene have been identified in many patients, more so in adult than childhood cases. *C-kit* encodes for *KIT*, the membrane receptor for stem cell factor, and is expressed on mast cells, melanocytes, and hematopoietic stem cells. These mutations likely contribute to the characteristic proliferation of mast cells and hyperpigmentation of the skin seen in cutaneous mastocytosis, as well as the myeloproliferative diseases observed in some patients with mastocytosis.⁹⁸

Diagnosis

The clinical presentation and characteristic cutaneous lesions usually allow for easy diagnosis. Skin biopsy should be performed when the diagnosis is unclear or when bullae are the main feature. Histopathologic criteria for the diagnosis of MIS include the presence of large clusters (15 cells each) of MCs or scattered MCs exceeding 20 cells per high-power ($\times 40$) field.⁹⁹ Toluidine blue, Giemsa or MC-specific stains for *c-kit* (CD117) and tryptase can assist with identification of MCs. Bullae, when present, are subepidermal. Baseline serum tryptase levels, which tend to correlate with BSA involvement, may be useful in predicting infants at high risk of serious systemic symptoms.⁹⁴ Clinical evidence of extracutaneous mastocytosis should guide any additional diagnostic studies (ultrasound, bone and liver/spleen scans, GI endoscopy, skeletal survey, and bone marrow evaluation).¹⁰⁰ The usefulness of studies performed empirically is limited, and they do not appear to provide any prognostic information.⁸⁷

Differential diagnosis

Mastocytomas should be differentiated from xanthomas, juvenile xanthogranulomas, café-au-lait macules and congenital nevi. Infestation with *Sarcoptes scabiei* presenting with pruritic, red-brown nodules that exhibit a Darier's sign may be mistaken for mastocytosis. Differentiating characteristics include more severe pruritus, lack of other lesions with other morphologies (e.g., paucity of macules and plaques commonly observed with MPCM), and distribution favoring covered and intertriginous areas in scabetic nodules.¹⁰¹ Where bullae are prominent or lesions are atypical, biopsy is indicated to differentiate mastocytosis from the immunobullous diseases, epidermolysis bullosa, or other infiltrative disorders (see Chapter 11).

Treatment and care

There is no curative treatment for pediatric mastocytosis, however the course in most cases is benign and the prognosis generally favorable. Solitary mastocytomas have not been reported to progress to systemic involvement.¹⁰⁰ More than 50% of childhood cases of MPCM/UP resolve by adolescence, and the remainder experience a marked reduction in cutaneous symptoms.^{91,102} Of the patients whose disease persists into adulthood, 15–30% develop indolent systemic involvement, which is similar to the rate observed in adult-onset disease.⁹¹

Children presenting with congenital bullous MPCM or DCM have a higher risk for sudden death, usually from circulatory collapse.¹⁰³

Treatment is aimed at reducing pruritus and, in some children, minimizing blister formation. The regular use of H₁ antihistamines such as hydroxyzine or cetirizine is effective in treating pruritus, bullae, flushing, and abdominal pain. The addition of H₂ blockers and oral disodium cromoglycate may be effective for patients with gastrointestinal signs or symptoms.^{104–106}

Cutaneous mastocytomas may be treated with a short course of ultra-potent topical steroids or topical calcineurin inhibitors, and very problematic lesions may be excised. Rare instances of circulatory collapse as a result of systemic histamine release should be treated with careful fluid management and intravenous epinephrine.¹⁰⁶ A self-injectable epinephrine device may be prescribed for children with a history of such episodes.⁸⁷ PUVA therapy is effective for severe forms of MIS.¹⁰⁷ Aggressive forms of MC respond partially to interferon- α or cladribine and there are positive anecdotal reports using tyrosine kinase inhibitors.⁹⁵ Parents should be provided with a list of substances that potentially stimulate mast cell activity and which should therefore be avoided or given with caution (Box 28.1).⁹⁰

INFANTILE SYSTEMIC HYALINOSIS AND JUVENILE HYALINE FIBROMATOSIS

Infantile systemic hyalinosis (ISH) and juvenile hyaline fibromatosis (JHF) are rare, progressive, autosomal recessive diseases. They are allelic and represent part of a spectrum, rather than two distinct entities. Clinical manifestations which are noted at birth or in early infancy include papular and nodular skin lesions (Fig. 28.15A), skeletal and soft tissue lesions, gingival hyperplasia (Fig. 28.15B), joint contractures (Fig. 28.15C), and growth retardation.

Cutaneous findings

Several distinct characteristic skin lesions are observed in JHF. Small, skin-colored, pearly papules are found predominantly on the ears, neck, and paranasal folds, where they may coalesce to form thin plaques (Fig. 28.15A). Translucent-appearing larger papules and nodules are found around the nose, behind the ears, and on the tips of digits. These may have a gelatinous consistency. Papillomatous perianal lesions, resembling condylomata, have been observed in some patients.¹⁰⁸

Extracutaneous findings

The most consistent and earliest extracutaneous manifestation of JHF is joint flexion contracture, especially of the knees and elbows. Many patients become severely disabled by these progressively severe contractures. Ultrasound evaluation of affected joints reveals distinctive alterations such as irregular cortical surface of MCPs and PIPs, osteophytes and bone erosions, and increased synovial fluid, even in infancy.¹⁰⁹ Gingival hypertrophy is seen in nearly all patients, and the majority have osteolytic bone lesions and osteoporosis.¹¹⁰ JHF generally does not involve the viscera; however, there is considerable clinical and histologic overlap with the more severe disease of infantile systemic hyalinosis (ISH). In ISH, there are hyaline deposits in multiple organs, recurrent infections, often persistent diarrhea, and death within the first 2 years of life.¹⁰⁸ Intellectual development is normal at both ends of the spectrum.

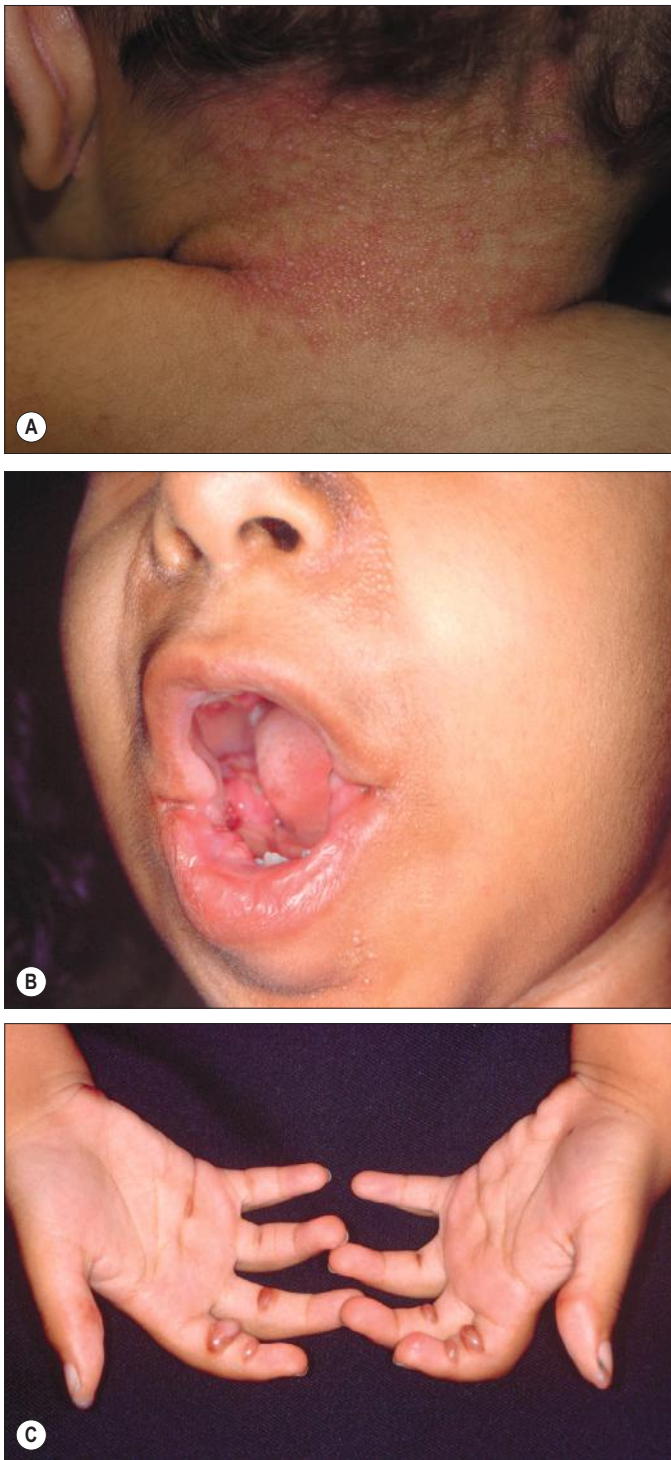


Figure 28.15 (A) Young child with juvenile hyaline fibromatosis with characteristic small papules on the nape. (B) A 7-year-old patient with juvenile hyaline fibromatosis. Gingival hypertrophy, fibromas of the vermillion and cutaneous lips, decreased oral aperture, and papules on the chin coalescing paranasally into small plaques are evident. (C) Same patient with fibromas of the fingers and hands with flexion contractures.

Etiology and pathogenesis

JHF and ISD are caused by mutations in the gene encoding capillary morphogenesis protein-2 (*CMG-2*), an integrin-like cell surface receptor for laminins and type IV collagen.^{111,112} The nature of the hyaline deposition is still not clear but may be

composed of increased type VI and decreased type I collagen.¹¹³ On routine histology, the dermal papules show thinning of the epidermis and a dermis occupied by abundant, amorphous, PAS-positive, diastase-resistant material containing wavy filamentous elements. Cells with oval or spindle-shaped nuclei are embedded in this stroma, imparting a chondroid appearance. These fibroblastic cells often display PAS-positive cytoplasmic vacuoles. Ultrastructurally, the fibroblastic stromal cells display a hyperplastic and dilated rough endoplasmic reticulum with collections of smooth-surfaced cisternae filled with tangled microfilaments.¹⁰⁸ Osteoporosis and osteolytic bone lesions are observed on radiographic examination of most patients. Routine laboratory evaluations are normal.

Differential diagnosis

The differential diagnosis should first include Winchester syndrome, a rare autosomal recessive condition that has many overlapping features with JHF, including joint contractures, dwarfism, hypertrophic lips and gingivae, severe osteoporosis, thickened leathery skin, and corneal opacities.¹¹⁴ Lipoid proteinosis may be distinguished from JHF by a distinctly different histology, a characteristic hoarse cry, and a more benign clinical course.

Treatment and course

The course is progressive. Excluding those most severely affected with hyaline material in the viscera, most patients survive into adulthood with severe physical deformities due to joint contractures, delayed motor development, and skin nodules that recur after surgical excision. Treatment, which is unsatisfactory, includes excision of skin lesions, repeated gingivectomy, and systemic corticosteroids for joint symptoms. At least one patient has been treated with interferon- α , with some reduction and softening of the smaller fibromas only (Ruiz-Maldonado and Duran, pers comm).

FARBER DISEASE

Farber disease, or Farber lipogranulomatosis, is a rare, progressive, autosomal recessive lysosomal storage disease that leads to the accumulation of ceramide in tissues. The disorder primarily involves the musculoskeletal, respiratory, integumentary, and nervous systems of affected infants, and onset occurs in the first year of life.¹¹⁵ It presents in early infancy with a characteristic clinical triad of subcutaneous nodules, progressive painful and deformed joints, and progressive hoarseness.

Cutaneous findings

The characteristic cutaneous features include multiple subcutaneous nodules, flesh-colored papules, nodules, or tumors, especially near joints. Coarse facial features and xanthoma-like papules on the face and hands have also been reported. The resultant granulomatous inflammatory lesions are common findings which may be due to decreased apoptosis of inflammatory cells secondary to increased intracellular ceramide.¹¹⁶

Extracutaneous findings

Painful, deforming joint swelling with restriction of movement, particularly of the distal interphalangeal and metacarpal joints, is characteristic. Infants frequently exhibit marked failure to thrive, recurrent infections, a hoarse cry attributed to laryngomalacia, dyspnea, noisy breathing, and hyperirritability.

Impairment of cognitive development, seizures, hepatosplenomegaly, macroglossia, recurrent fevers, and hyporeflexia are variably present.

Etiology and pathogenesis

Farber lipogranulomatosis is caused by a mutation in the gene *ASAHI*, which encodes for lysosomal acid ceramidase, with resultant progressive accumulation of ceramide in tissues. The characteristic clinical presentation and the detection of low levels of acid ceramidase are diagnostic of Farber disease. Light microscopic examination of skin and other affected tissues is nonspecific, demonstrating foam cells and a granulomatous infiltrate. This inflammation is hypothesized to be due to altered receptor-mediated apoptosis by intracellular ceramide accumulation.¹¹⁷ Several characteristic structures are observed ultra-microscopically, probably resulting from the accumulation of ceramide in cells. Curvilinear tubular bodies (comma-shaped, tubular structures consisting of two single membranes separated by a clear space) are observed in dermal fibroblasts among other affected cells. Banana bodies (variably membrane-bound structures that have a spindle and usually curved shape) are found predominantly in Schwann cells of peripheral nerves.¹¹⁶

Diagnosis

Radiologic examination reveals diffuse osteopenia, underdevelopment of terminal phalanges, and reduced long bone diameters.¹¹⁷ The diagnosis should be confirmed by detection of deficient lysosomal acid ceramidase activity in leukocytes, fibroblasts, or other tissues.

Differential diagnosis

The differential diagnosis includes metabolic storage diseases, particularly other mucopolidoses, malignant histiocytosis, and infantile systemic hyalinosis. Some cases have been misdiagnosed as juvenile rheumatoid arthritis because of the severe joint involvement seen early in the course.

Treatment and course

Most patients die of progressive neurologic deterioration early in the first decade of life. Hematopoietic stem cell transplantation was successfully performed in four patients without CNS involvement (type 2/3 disease), but allogeneic bone marrow transplant failed to halt the progression of Farber disease with CNS involvement (type 1).¹¹⁷ Various other treatments, including corticosteroids and radiotherapy, have been attempted and are ineffective. The potassium–titanyl–phosphate (KTP) laser has been used for treatment of severe oral lesions.¹¹⁸

Because transmission is autosomal recessive, genetic counseling is mandatory. Prenatal diagnosis, performed by assaying acid ceramidase levels in skin cells cultured from amniotic fluid, is now possible.¹¹⁹

MUCOPOLYSACCHARIDOSES

The mucopolysaccharidoses (MPS) are a heterogeneous group of rare lysosomal storage disorders that display several variable clinical features, including coarse facies, skeletal abnormalities, mental retardation, corneal clouding, and hepatosplenomegaly. The degree of progression varies among the diseases, as does the constellation of clinical and laboratory findings. Each disease results from the deficiency of one specific lysosomal enzyme, but all are characterized by accumulation of

mucopolysaccharides (glycosaminoglycans) in lysosomes and excessive amounts of mucopolysaccharides in the urine.¹²⁰ Sanfilippo syndrome is the most common, and has an incidence of about 1 : 25 000. This is contrasted with Sly syndrome, of which only 40 cases have been reported worldwide.¹²¹

Cutaneous findings

The most characteristic cutaneous feature, manifest in all types of MPS, is coarse, thickened skin. This cutaneous alteration combines with underlying craniofacial abnormalities to impart coarse facial features. Patients have a thick nose with a depressed nasal bridge, thick tongue and lips, short neck, and macrocephaly. The severity of the facial abnormalities is variable, and the most striking features are observed in Hurler and Hunter syndromes. Coarse facies may not be present in young infants.¹²² Patients also display variable degrees of coarse hair and generalized hirsutism.

Apart from Sanfilippo syndrome, which presents with synophrys, Hunter syndrome is the only MPS that regularly presents with specific cutaneous findings. Children with Hunter syndrome may develop firm, discrete or coalescing ivory-colored papules on the arms or symmetrically distributed between the angles of the scapulae and the posterior axillary lines. This same finding was described in a patient with Hurler–Scheie syndrome.¹²³ Another finding occasionally reported in Hunter syndrome is usually widespread dermal melanocytosis (see [Chapter 24](#)).

Extracutaneous findings

Infants may appear normal at birth, but usually develop characteristic findings in the first few years of life. Each disease has its own array of clinical findings; however, the most important extracutaneous features are mental retardation, deafness, hyperactivity/behavior problems, stiff joints, skeletal dysplasia, kyphoscoliosis, corneal clouding, valvular and coronary heart disease, hepatosplenomegaly, noisy breathing, and lower respiratory tract infections. [Table 28.1](#) lists the cardinal characteristics and pertinent negative findings for each disorder. The skeletal abnormalities in the MPS are referred to as dysostosis multiplex and comprise the following elements: large, thickened skull with premature closure of lambdoid and sagittal sutures; shallow orbits; enlarged J-shaped sellae; and anterior hypoplasia of the lumbar vertebrae. In addition, the long bones display enlarged diaphyses, irregular metaphyses, and poor development of the epiphyseal centers.

Etiology and pathogenesis

Each type of MPS is caused by a deficiency of a specific lysosomal enzyme responsible for the degradation of mucopolysaccharides. This deficiency results in excessive accumulation of the mucopolysaccharides: dermatan sulfate, heparan sulfate, and keratan sulfate throughout the body. The deficient enzyme has been elucidated for each disease, and the genetic loci for several have been mapped.¹²⁴ All have an autosomal recessive inheritance, except for Hunter syndrome, which is X-linked recessive. Excluding an increased incidence of Hunter syndrome in the Jewish population in Israel, and Morquio syndrome in French-Canadians, MPS appear to affect all ethnic groups equally.

Diagnosis

The testing of urine for glycosaminoglycans is the basis for screening patients suspected of having MPS. If screening tests

TABLE
28.1

Classification and features of the mucopolysaccharidoses

Eponym	MPS number	Main clinical features (and pertinent negatives)	Urinary mucopolysaccharide
Hurler	I-H	IH, UH, HSM, SS, JS, URI, MR, HL, HD, DM, CC, Hc	DS, HS
Hurler–Scheie	I-H/S	HL, JS, CC, HD, Mg, no MR	DS, HS
Scheie	I-S	JS, HD, CC, no MR, no SS	DS, HS
Hunter (severe)	II-A	SP, IH, UH, HSM, SS, JS, URI, MR, HL, DM, RD, Hc, no CC	DS, HS
Hunter (mild)	II-B	SP, HL, JS, HD, mild CC, no MR	DS, HS
Sanfilippo	III A–D	MR (onset 3–4 years), mild HSM, mild DM, synophrys	HS ^b
Morquio (classic)	IV-A	SD, SS, CC, no MR	KS
Maroteaux–Lamy	VI	IH, UH, SS, JS, URI, HD, HSM, HLHc, DM, CC, no MR	DS
Sly	VII	IH, UH, HSM, SS, JS, URI, MR, HL, HD, Hc, DM, CC ^c	DS, HS

CC, corneal clouding; DM, dysostosis multiplex; DS, dermatan sulfate; Hc, hydrocephalus; HD, heart disease; HL, hearing loss; HS, heparan sulfate; HSM, hepatosplenomegaly; IH, inguinal hernia; JS, joint stiffness; KS, keratan sulfate; Mg, micrognathism; MR, mental retardation; RD, retinal degeneration; SD, spondyloepiphyseal dysplasia; SP, skin papules; SS, short stature; UH, umbilical hernia; URI, upper respiratory tract infections.

^aSome subtypes omitted. ^bMay be missed due to small amount. ^cLarge variability of phenotypes observed.

are positive for glycosaminoglycans, a quantitative analysis should be performed to confirm the presence of MPS. The type and quantity of urinary glycosaminoglycans, combined with the child's clinical presentation, are used to determine the most appropriate enzyme assay to establish definitively the specific type of MPS.¹²⁰ The enzymatic diagnosis should be determined in all patients in whom MPS is suspected. Lysosomal enzyme analysis may be carried out using serum, leukocytes, or cultured cells. In all the MPS, histopathologic examination of skin with Alcian blue, colloidal iron, or Giemsa stain reveals metachromatic granules in fibroblasts, and occasionally in keratinocytes, and in the secretory and ductal cells of eccrine glands. In addition, the cutaneous papules, mostly seen in Hunter syndrome, exhibit extracellular dermal deposits of metachromatic material.¹²⁴

Differential diagnosis

The mucopolipidoses are the most important group of diseases to be differentiated from the MPS. I-cell disease (mucopolipidosis II) shares most of the clinical features of Hurler syndrome, but patients with I-cell disease do not exhibit urine mucopolysaccharides or acceleration of skeletal growth around 1 year of age.

Treatment, course, and management

The natural course of the more severe forms is progressive, and death resulting from respiratory or cardiac complications often occurs during the second decade. Some types, such as Scheie syndrome, have a normal life expectancy. Bone marrow transplantation lessens the severity and slows the progression of most cases.^{121,125} Treatment of patients with MPS I using enzyme replacement therapy with recombinant human α -L-iduronidase reduces lysosomal storage in the liver and levels of urinary glycosaminoglycan excretion, and improves respiratory function and exercise tolerance.^{126,127} Because this enzyme does not cross the blood–brain barrier, most likely it will not influence the central nervous manifestations.¹²⁸

Otherwise, management revolves around supportive care. Physical therapy and nighttime splinting may prevent contractures. Special education and frequent audiologic evaluation should be instituted. Many patients benefit from hearing aids. Echocardiograms are recommended to evaluate for valvular abnormalities. Surgical interventions, including corneal transplants for cloudy corneas, cardiac valve replacement, ventriculoperitoneal shunts for communicating hydrocephalus, tracheostomies for obstructive sleep apnea, and occasionally

herniorrhaphies, may be helpful. Patients may possess atlantoaxial joint instability imparting an increased risk for spinal injury and paralysis. All patients at risk should undergo careful evaluation, and spinal fusion is recommended for those who are severely affected. Prenatal diagnosis is performed by enzyme assays of cultured amniotic cells, or of cells obtained in chorionic villus sampling.¹²⁹ Prenatal genetic mutational analysis is used less frequently.

I-CELL DISEASE

I-cell disease, or mucopolipidosis II, is a rare autosomal recessive storage disorder due to faulty lysosomal enzyme transport. The skeletal and central nervous systems are most severely affected, but characteristic skin changes also occur. I-cell disease exhibits signs and symptoms of both mucopolysaccharidoses (particularly Hurler syndrome), and sphingolipidoses. The term I-cell, or inclusion cell, refers to the presence of cytoplasmic inclusions associated with lysosomes. Onset occurs at birth, and disease progression results in death during the first decade.

Cutaneous findings

The most notable cutaneous findings are the facial features: small orbits and prominent eyes, thickening of the eyelids with a prominent venous pattern, and fullness of the lower face with rounded cheeks. Many small telangiectasias impart a ruddy appearance to the cheeks. Patients often exhibit a fish-mouth appearance in profile as a result of prominent maxillary bones. The neck is short, and the skin has a thickened and rigid texture, particularly on the neck and ears. Gingival hypertrophy, not present in Hurler syndrome, is progressive and severe. At least one patient presented with blueberry muffin rash.¹³⁰

Extracutaneous findings

Neonates commonly exhibit intrauterine growth retardation, with birthweights often below 2500 g. Linear growth is below normal and ceases at 1 year of age. Orthopedic problems manifesting as dysostosis multiplex are common presenting features. Inguinal hernias, especially in boys, may be noted at birth, and patients of both sexes have frequent upper respiratory tract infections and hepatosplenomegaly. All patients experience severe psychomotor retardation, and the majority neither walk unaided nor develop more than primitive language skills. There is progressive stiffness of all joints, first apparent in the shoulders, with decreased mobility by 2 years of age.¹³¹ The long

bones of affected infants younger than 6 months display periosteal cloaking, possibly due to repeated new bone formation, and some are born with congenitally short femurs or present with findings suggestive of rickets.¹³² Cone-shaped phalanges and abnormalities of the skull and pelvis are also observed.¹³³

Etiology and pathogenesis

I-cell disease is caused by mutations in the *GlcNAc-phosphotransferase alpha/beta* gene resulting in defective *N*-acetyl-glucosamine-1-phosphotransferase, an enzyme involved in the synthesis of a mannose-6-phosphate marker of hydrolases normally found in lysosomes. Because newly synthesized lysosomal enzymes are not marked correctly, the mannose-6-phosphate receptor-dependent transport fails, and the enzymes are secreted out of cells instead of being targeted to lysosomes. This results in failed lysosomal degradation of macromolecules, simulating a catabolic enzyme defect.¹³⁴ Fibroblast lysosomal enzymes are deficient in patients with I-cell disease, whereas the serum levels of the same enzymes are markedly elevated.¹³⁵ The finding that some tissues have normal levels of lysosomal enzymes suggests that there may be an alternative method for targeting lysosomal hydrolases in these tissues.¹³⁶

Diagnosis

The diagnosis of I-cell disease is suggested by detection of an increase in the activity of several hydrolases in plasma. It is confirmed by dermal fibroblast cultures, which show the characteristic cytoplasmic inclusions (I-cells) in the cultured cells. These cytoplasmic inclusions stain positively for PAS and Sudan black, but negatively for Alcian blue, suggesting that the inclusion bodies represent an abnormal accumulation of glycolipid.¹³³ Reduced activity of lysosomal hydrolases in the fibroblasts provides additional confirmation of the diagnosis. Mutational analysis of the *GlcNAc-phosphotransferase alpha/beta* gene is also possible.

Differential diagnosis

I-cell disease shares most of the clinical features of Hurler syndrome, including coarse facial features, severe psychomotor retardation, and skeletal dysplasia. However, patients with I-cell disease do not exhibit mucopolysaccharides in their urine. Gingival hypertrophy and vacuolated peripheral blood lymphocytes, characteristic of I-cell disease, are not present in Hurler disease.

Treatment and course

Death in early childhood is usually secondary to pulmonary infection or congestive heart failure. Bone marrow transplantation appears to slow neurologic and cardiac progression, but does not alter the skeletal disease.¹³⁷ Because of the recessive inheritance pattern, genetic counseling should be offered. Successful prenatal diagnosis has been accomplished by demonstrating elevated enzyme levels in amniotic fluid in conjunction with enzyme assays from cultured amniotic fluid cells and by electron microscopy showing marked vacuolation in chorionic villus cells.^{138,139}

LIPOID PROTEINOSIS

Lipoid proteinosis (hyalinosis cutis et mucosae, or Urbach-Wiethe syndrome) is a rare, nonfatal, autosomal recessive disorder characterized by deposition of amorphous hyaline

material around dermal blood vessels. Cutaneous lesions progress from infancy throughout childhood and become characteristic for this disease by adulthood. Even though any system can be involved, the upper aerodigestive tract, skin, and central nervous system are most commonly affected.

Cutaneous findings

The cutaneous lesions are rarely present at birth but tend to occur in the first few years of life. Initially they have varied morphologies, such as erosions, small blisters, crusts and thin papules, which may have features suggestive of impetigo, acne, or varicella. These lesions subsequently develop hypertrophic, and less often atrophic, scarring. Over time the face and trauma-prone sites develop yellowish infiltrated papules and nodules and scarring, reminiscent of cutaneous changes observed with porphyria. Scalp lesions may result in scarring alopecia and significant pruritus can be a problem in some. By about 8 years the majority of patients will display the characteristic small beaded papules along the eyelid margins (moniliform blepharosis) and lips.¹⁴⁰ In addition to these findings, less distinctive firm papules may develop on the neck, armpits, hands, elbows, and knees. Similar lesions may involve the oral mucosa, with resultant loss of teeth and various degrees of ankyloglossia.

Extracutaneous findings

Hoarseness and a weak cry secondary to thickened vocal cords may be present at birth and are usually the first signs of the disease. Even though virtually every organ has been reported to be involved, lipoid proteinosis runs a chronic nonfatal course. Apart from the laryngeal and mucosal involvement, the central nervous system is most commonly affected, resulting in seizures or behavioral changes. Prominent corneal nerves noted with slit lamp examination and confocal microscopy are observed even before moniliform blepharosis.¹⁴¹ Frequently, intracranial calcifications, most often in the temporal lobes, are noted on radiographs from affected individuals.

Etiology and pathogenesis

Pathogenic loss-of-function mutations have been found in the extracellular matrix protein 1 gene (*ECM1*).¹⁴² The glycoprotein extracellular matrix protein 1 functions in keratinocyte differentiation, basement membrane integrity, and collagen fibril macroassembly. It is recognized also as an autoantigen target in patients with lichen sclerosis et atrophicus.

Diagnosis and differential diagnosis

Routine histology of affected skin demonstrates deposition of amorphous eosinophilic, PAS-positive, hyaline-like material forming concentric rings around microvasculature of the dermis. The mucosa, especially the larynx, and internal organs may likewise be affected. Ultrastructurally, there is disruption and reduplication of the basement membrane around blood vessels and at the dermoepidermal junction. Lipoid proteinosis must first be differentiated from erythropoietic protoporphyria. Lesions in sun-protected and mucosal sites when porphyrin levels are normal assist in this distinction. Other diseases to consider in the differential include papular mucinosis, amyloidosis, cutaneous xanthomas, and leprosy. The rare finding of persistent hoarseness in infancy should be differentiated from congenital hypothyroidism, congenital dysphonia, junctional epidermolysis bullosa, and Farber lipogranulomatosis (see above).

Treatment, course, and management

There is no generally accepted treatment. Mucosal stripping of the vocal cords can temporarily relieve hoarseness, and dermabrasion and CO₂ laser have been performed on skin and vocal cord lesions, respectively.¹⁴³ Dimethyl sulfoxide, D-penicillamine and etretinate therapy have been attempted with varying responses.¹⁴⁴ The overall course is generally benign, with progression throughout childhood and stabilization in early adulthood; therefore supportive care is a rational approach.

CUTANEOUS MUCINOSIS OF INFANCY

Cutaneous mucinosis (CM) is a term encompassing various disorders in which the most prominent feature is deposition of mucin in the skin. CM can be categorized as primary or secondary and diffuse or focal and include entities such as myxedema, lichen myxedematosus (papular mucinosis), alopecia mucinosis, cutaneous myxoid cysts, cutaneous focal mucinosis, self-healing juvenile cutaneous mucinosis, mucinous nevus and cutaneous mucinosis of infancy. All are rare and the only disorders likely to be encountered in the neonate or infant are cutaneous mucinosis of infancy (CMI) and mucinous nevus. The first case of CMI was reported by Lum in 1980. This infant developed skin lesions at 4 months of age.¹⁴⁵ Since, there have been fewer than 10 cases of CMI reported in the English literature. Rongioletti chronicled the entire clinicopathologic spectrum from CMI to papular mucinosis within a single patient and surmised that CMI may not be a distinct disorder, but an infantile manifestation of papular mucinosis.¹⁴⁶

Cutaneous findings

Skin lesions can be variable but the typical presentation is that of firm, skin-colored to opalescent papules on the upper arms, dorsal hands and trunk. The lesions can be symmetrical and tightly

grouped, linear and in rows, or more generalized. They usually appear soon after birth but can be congenital. Histological findings of lesions demonstrate focal, well-circumscribed deposits of mucin composed of hyaluronic acid (positive stains for Alcian blue at pH 2.5 and colloidal iron) superficially located in the papillary dermis with no evidence of an increase in fibrocytes. A perivascular mononuclear cell infiltrate is also seen in the superficial dermis.

Extracutaneous findings

Laboratory evaluation for paraproteinemia (elevated in scleromyxedema), thyroid function studies (abnormal in myxedema), and autoimmunity are normal or negative. There are no systemic associations typically observed with either CMI or mucinous nevus. One patient with CMI had developmental delay, congenital cataracts, inguinal hernias, and an accessory tragus of unclear etiology.

Etiology and pathogenesis

The etiology and pathogenesis is unknown for CMI.

Diagnosis and differential diagnosis

When congenital CMI needs to be distinguished from the hamartomatous mucinous nevus, it is generally a larger lesion that presents with multiple skin-colored to brownish papules and plaques in a strikingly unilateral Blaschkoid distribution. The histology differs in that there are homogeneous, band-like mucin deposits in the upper portion of the dermis.

Treatment, course, and management

The rarity of CMI precludes any acknowledged treatment recommendation. However, lesions appear to be unresponsive to high-potency topical corticosteroids or tretinoin cream.

Access the full reference list at ExpertConsult.com 

KEY REFERENCES

23. Holland KE, Galbraith SS, Drolet BA. Neonatal violaceous skin lesions: expanding the differential of the 'blueberry muffin baby'. *Adv Dermatol* 2005;21:153–92.
35. Haupt R, Minkov M, Astigarraga I, et al. Langerhans cell histiocytosis (LCH): Guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. *Pediatr Blood Cancer* 2013;60:175–84.
49. Ferrari A, Orbach D, Sultan I, et al. Neonatal soft tissue sarcomas. *Semin Fetal Neonatal Med* 2012;17:231–8.
75. Cordoro KM, Gupta D, Frieden IJ, et al. Pediatric melanoma: Results of a large cohort study and proposal for modified ABCD detection criteria for children. *J Am Acad Dermatol* 2013;68(6):913–25.
90. Ahmad N, Evans P, Lloyd-Thomas AR. Anesthesia in children with mastocytosis – a case based review. *Pediatr Anesth* 2009;19: 97–107.
94. Kettelhut BV, Metcalfe DD. Plasma histamine concentration in the evaluation of pediatric mastocytosis. *J Pediatr* 1987;111:419–21.
96. Alvarez-Twose I, Vañó-Galván S, Sánchez-Muñoz L, et al. Increased serum baseline tryptase levels and extensive skin involvement are predictors for the severity of mast cell activation episodes in children with mastocytosis. *Allergy* 2012;67:813–21.
97. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25(7): 603–25.
102. Azana MJ, Torrelo A, Mediero IG, et al. Urticaria pigmentosa: A review of 67 pediatric cases. *Pediatr Dermatol* 1994;11:102–6.
146. Podda M, Rongioletti F, Greiner D, et al. Cutaneous mucinosis of infancy: is it a real entity or the paediatric form of lichen myxoedematosus (papular mucinosis)? *Br J Dermatol* 2001;144(3):590–3.

REFERENCES

- Isaacs H. Cutaneous metastases in neonates: a review. *Pediatr Dermatol* 2011;28:85–93.
- Fender AB, Gust A, Wang N. Congenital leukemia cutis. *Pediatr Dermatol* 2008;25:34–7.
- Francis JS, Sybert VP, Benjamin DR, et al. Congenital monocytic leukemia: Report of a case with cutaneous involvement, and review of the literature. *Pediatr Dermatol* 1989;6:306–11.
- Resnik KS, Brod BB. Leukemia cutis in congenital leukemia. *Arch Dermatol* 1993;129:1301–6.
- van der Linden MH, Creemers S, Pieters R. Diagnosis and management of neonatal leukaemia. *Semin Fetal Neonatal Med* 2012;17:192–5.
- Lestringant GG, Masouye I, El-Hayek M, et al. Diffuse calcinosis cutis in a patient with congenital leukemia and leukemia cutis. *Dermatology* 2000;200:147–50.
- Gottesfeld E, Silverman A, Coccia PF, et al. Transient blueberry muffin appearance of a newborn with congenital monoblastic leukemia. *J Am Acad Dermatol* 1989;21:347–51.
- Yen A, Sanchez R, Oblender M, et al. Leukemia cutis: Darier's sign in a neonate with acute lymphoblastic leukemia. *J Am Acad Dermatol* 1996;34:375–8.
- Bhatt S, Schreck R, Graham JM, et al. Transient leukemia with trisomy 21: Description of a case and review of the literature. *Am J Genet* 1995;58:310–14.
- Solky BA, Yang CF, Xu X, et al. Transient myeloproliferative disorder causing a vesiculopustular eruption in a phenotypically normal neonate. *Pediatr Dermatol* 2004;21:551.
- Viros A, Garcia-Patos V, Aparicio G, et al. Sterile neonatal pustulosis associated with transient myeloproliferative disorder in twins. *Arch Dermatol* 2005;141:1053–4.
- van den Berg H, Hopman AH, Kraakman KC, et al. Spontaneous remission in congenital leukemia is not related to (mosaic) trisomy 21: case presentation and literature review. *Pediatr Hematol Oncol* 2004;21:135–44.
- Dinulos JG, Hawkins DS, Clark BS, et al. Spontaneous remission of congenital leukemia. *J Pediatr* 1997;131:300–3.
- Eberst E, Michel B, Stoeber P. Spontaneous remission of congenital leukemia cutis. *Ann Dermatol Venereol* 2011;138:586–90.
- Rénard C, Girard S, Pracros JP. Granulocytic sarcoma, a diagnostic challenge: 3 pediatric cases. *Arch Pediatr* 2010;17:149–53.
- Minkov M, Prosch H, Steiner M, et al. Langerhans cell histiocytosis in neonates. *Pediatr Blood Cancer* 2005;45: 802–7.
- Stein SL, Paller AS, Haut R, et al. Langerhans cell histiocytosis presenting in the neonatal period: a retrospective case series. *Arch Pediatr Adolesc Med* 2001;155:778–83.
- Stiakaki E, Giannakopoulou C, Kouvidi E, et al. Congenital systemic Langerhans' cell histiocytosis (Report of two cases). *Haematologia* 1997;28:215–22.
- Esterly NB, Maurer HS, Gonzalez-Crussi F. Histiocytosis X: A seven-year experience at a children's hospital. *J Am Acad Dermatol* 1985;13:481–96.
- Enjolras O, Leibowitch M, Bocanini F, et al. Congenital cutaneous Langerhans' cell histiocytosis: a seven cases report. *Ann Dermatol Venereol* 1992;119:111–17.
- The French Langerhans' Cell Histiocytosis Study Group. A multicentre retrospective survey of Langerhans' cell histiocytosis: 348 cases observed between 1983 and 1993. *Arch Dis Child* 1996;75:17–24.
- Munn S, Chu AC. Langerhans' cell histiocytosis of the skin. *Hematol Oncol Clin North Am* 1998;12:269–86.
- Holland KE, Galbraith SS, Drolet BA. Neonatal violaceous skin lesions: expanding the differential of the 'blueberry muffin baby'. *Adv Dermatol* 2005;21:153–92.
- Shaffer MP, Walling HW, Stone MS. Langerhans' cell histiocytosis presenting as blueberry muffin baby. *J Am Acad Dermatol* 2005;53: S143–6.
- De Berker D, Lever LR, Windebank K. Nail features in Langerhans' cell histiocytosis. *Br J Dermatol* 1994;130:523–7.
- Hashimoto K, Pritzker MS. Electron microscopic study of reticulohistiocytoma; an unusual case of congenital, self-healing reticulohistiocytosis. *Arch Dermatol* 1973;107:263–70.
- Ricciardo B, Irvine A, McDermott M, et al. A case of congenital solitary Langerhans cell histiocytoma. *Australas J Dermatol* 2011;52: e1–3.
- Herman LE, Rothman KE, Harawi S, et al. Congenital self-healing reticulohistiocytosis. *Arch Dermatol* 1990;126:210–12.
- Hashimoto K, Takahashi S, Lee RG, et al. Congenital self-healing reticulohistiocytosis. *J Am Acad Dermatol* 1984;11:447–54.
- Kapila PK, Grant-Kels JM, Allred C, et al. Congenital, spontaneously regressing histiocytosis: Case report and review of the literature. *Pediatr Dermatol* 1985;2:312–17.
- Schmitz L, Favara BE. Nosology and pathology of Langerhans' cell histiocytosis. *Hematol Oncol Clin North Am* 1998;12:221–47.
- Longaker MA, Frieden IJ, LeBoit PE, et al. Congenital 'self-healing' Langerhans' cell histiocytosis: the need for long term follow-up. *J Am Acad Dermatol* 1994;31:910–16.
- Arico M, Egeler RM. Clinical aspects of Langerhans' cell histiocytosis. *Hematol Oncol Clin North Am* 1998;12:247–58.
- Geissmann F, Thomas C, Emile JF, et al. Digestive tract involvement in Langerhans' cell histiocytosis. The French Langerhans' Cell Histiocytosis Study Group. *J Pediatr* 1996;129: 836–45.
- Haupt R, Minkov M, Astigarraga I, et al. Langerhans cell histiocytosis (LCH): Guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. *Pediatr Blood Cancer* 2013;60:175–84.
- Tsianakas A, Kienast AK, Hoeger PH. Infantile-onset cutaneous T-cell lymphoma. *Br J Dermatol* 2008;159:1338–41.
- Ben Barak A, Elhasid R, Ben Itzhak O, et al. Infant anaplastic lymphoma: case report and review of the literature. *Pediatr Hematol Oncol* 2007;24:379–85.
- de Souza A, Camilleri MJ, Wada DA, et al. Clinical, histopathologic, and immunophenotypic features of lymphomatoid papulosis with CD8 predominance in 14 pediatric patients. *J Am Acad Dermatol* 2009;61:993–1000.
- Trupiano JK, Bringelsen K, Hsi ED. Primary cutaneous lymphoblastic lymphoma presenting in an 8-week old infant. *J Cutan Pathol* 2002;29:107–12.
- Fink-Puches R, Chott A, Ardigó M, et al. The spectrum of cutaneous lymphomas in patients less than 20 years of age. *Pediatr Dermatol* 2004;21:525–33.
- Kawachi Y, Jun-Ichi F, Yashuhiro F et al. Indolent subcutaneous panniculitis-like T cell lymphoma in a 1-year-old child. *Pediatr Dermatol* 2012;29:374–7.
- Boccaro O, Blanche S, de Prost Y et al. Cutaneous hematologic disorders in children. *Pediatr Blood Cancer* 2012;58:226–32.
- Janka G, zur Stadt U. Familial and acquired hemophagocytic lymphohistiocytosis. *Hematology Am Soc Hematol Educ Program* 2005: 82–8.
- Henter J-I, Arico M, et al. Familial hemophagocytic lymphohistiocytosis. *Hematol Oncol Clin North Am* 1998;12:417–33.
- Woods CW, Bradshaw WT, Woods AG. Hemophagocytic lymphohistiocytosis in the premature neonate. Hemophagocytic lymphohistiocytosis in the premature neonate. *Adv Neonatal Care* 2009 9:265–73.
- Soule EH, Pritchard DJ. Fibrosarcoma in infants and children. *Cancer* 1977;40:1711–21.
- Balsaver AM, Butler JJ, Martin RG. Congenital fibrosarcoma. *Cancer* 1967;20:1607–16.
- Chung EB, Enzinger FM. Infantile fibrosarcoma. *Cancer* 1976;38:729–39.
- Ferrari A, Orbach D, Sultan I, et al. Neonatal soft tissue sarcomas. *Semin Fetal Neonatal Med* 2012;17:231–8.
- Hayward PG, Orgill DP, Mulliken JB, et al. Congenital fibrosarcoma masquerading as lymphatic malformation: report of two cases. *J Pediatr Surg* 1995;30:84–8.
- Boon LM, Fishman SJ, Lund DP, et al. Congenital fibrosarcoma masquerading as congenital hemangioma: report of two cases. *J Pediatr Surg* 1995;30:1378–81.
- Muzaffar AR, Friedrich JB, Lu KK, et al. Infantile fibrosarcoma of the hand associated with coagulopathy. *Plast Reconstr Surg* 2006;117: e81–6.
- Neifeld JP, Berg JW, Godwin D, et al. A retrospective epidemiologic study of pediatric fibrosarcomas. *J Pediatr Surg* 1978;13:735–9.
- Ferguson WS. Advances in the adjuvant treatment of infantile fibrosarcoma. *Exp Rev Anticancer Ther* 2003;3:185–91.
- Loh ML, Ahn P, Perez-Atayde AR, et al. Treatment of infantile fibrosarcoma with chemotherapy and surgery: results from the Dana-Farber Cancer Institute and Children's Hospital, Boston. *J Pediatr Hematol Oncol* 2002;24:722–6.
- Kahn TA, Liranzo MO, Vidimos AT, et al. Pathological case of the month. *Arch Pediatr Adolesc Med* 1996;150:549–50.
- Annessi G, Cimitan A, Girolomoni G, et al. Congenital dermatofibrosarcoma protuberans. *Pediatr Dermatol* 1993;10:40–2.
- Maire G, Fraïtag S, Galmiche L, et al. A clinical, histologic, and molecular study of 9 cases of congenital dermatofibrosarcoma protuberans. *Arch Dermatol* 2007;143:203–10.
- Terrier-Lacombe MJ, Guillou L, Maire G, et al. Dermatofibrosarcoma protuberans, giant cell fibroblastoma, and hybrid lesions in children: clinicopathologic comparative analysis of 28 cases with molecular data – a study from the French Federation of Cancer Centers Sarcoma Group. *Am J Surg Pathol* 2003;27:27–39.
- McKee PH, Fletcher CD. Dermatofibrosarcoma protuberans presenting in infancy and childhood. *J Cutan Pathol* 1991;18:241–6.

61. Hobbs ER, Wheeland RG, Bailin PL, et al. Treatment of dermatofibrosarcoma protuberans with Mohs micrographic surgery. *Ann Surg* 1988;207:102–7.
62. Fisher PG, Reynolds P, Von Behren J, et al. Cancer in children with nonchromosomal birth defects. *J Pediatr* 2012;160(6):978–83.
63. Hawthorne HC, Nelson JS, Witzleben CL, et al. Blanching subcutaneous nodules in neonatal neuroblastoma. *J Pediatr* 1970;77:297–300.
64. Lucky AW, McGuire J, Komp DM. Infantile neuroblastoma presenting with cutaneous blanching nodules. *J Am Acad Dermatol* 1982;6:389–91.
65. Boyd TK, Schofield DE. Monozygotic twins concordant for congenital neuroblastoma: Case report and review of the literature. *Pediatr Pathol Lab Med* 1995;15:931–40.
66. Brodeur GM, Prithcard J, Berthold F. Revisions of the international criteria of neuroblastoma diagnosis. *J Clin Oncol* 1993;11:1466–77.
67. De Giovanni C, Landuzzi C, Nicoletti G, et al. Molecular and cellular biology of rhabdomyosarcoma. *Future Oncol* 2009;5:1449–75.
68. Yang P, Grufferman S, Khoury MJ, et al. Association of childhood rhabdomyosarcoma with neurofibromatosis type I and birth defects. *Gen Epidemiol* 1995;12:467–74.
69. Ilyas EN, Goldsmith K, Lintner R, et al. Rhabdomyosarcoma arising in a giant congenital melanocytic nevus. *Cutis* 2004;73:39–43.
70. Wiss K, Solomon A, Raimer S, et al. Rhabdomyosarcoma presenting as a cutaneous nodule. *Arch Dermatol* 1988;124:1687.
71. Issacs H. Fetal and neonatal rhabdoid tumor. *J Pediatr Surg* 2010;45:619–26.
72. Maurer HM, Gehan EA, Hayes DM, et al. The Intergroup Rhabdomyosarcoma Study II. *Cancer* 1993;71:1904–22.
73. Ceballos PI, Ruiz-Maldonado R, Mihm MC. Melanoma in children. *N Engl J Med* 1995;332:656–62.
74. Trozak DJ, Rowland WD, Hu F. Metastatic malignant melanoma in prepubertal children. *Pediatr Clin* 1973;191–204.
75. Cordero KM, Gupta D, Frieden IJ, et al. Pediatric melanoma: Results of a large cohort study and proposal for modified ABCD detection criteria for children. *J Am Acad Dermatol* 2013;68(6):913–25.
76. Prose NS, Laude TA, Heilman ER, et al. Congenital malignant melanoma. *Pediatrics* 1987;79:967–70.
77. Ruiz-Maldonado R, Orozco-Covarrubias L. Malignant melanoma in children. *Arch Dermatol* 1997;133:363–71.
78. Narayasingh V, Busby GO. Congenital malignant melanoma. *J Pediatr Surg* 1986;21:81–2.
79. Schneiderman H, Wu AY, Campbell WA. Congenital melanoma with multiple prenatal metastases. *Cancer* 1987;60:1371–7.
80. Cavell B. Transplacental metastasis of malignant melanoma. *Acta Pediatr* 1963;146:37–40.
81. Paradela S, Fonseca E, Pita-Fernandez S, et al. Spitzoid and non-spitzoid melanoma in children. A prognostic comparative study. *J Eur Acad Dermatol Venereol* 2013;27(10):1214–21.
82. Pol-Rodriguez M, Shing L, Silvers DN, et al. Influence of age on survival in childhood spitzoid melanomas. *Cancer* 2007;109:1579–83.
83. Hendrickson MR, Ross JC. Neoplasms arising in giant congenital nevi. Morphologic study of seven cases and a review of the literature. *Am J Surg Pathol* 1981;5:109–35.
84. Silvers DN, Helwig EB. Melanocytic nevi in neonates. *J Am Acad Dermatol* 1981;4:166–75.
85. April MM, Ward RE, Garelick JM. Diagnosis, management, and follow-up of congenital head and neck teratomas. *Laryngoscope* 1998;108:1398–401.
86. Mullen M, Rabban J, Frieden IH. Sacrococcygeal teratoma masquerading as congenital hemangioma. *Pediatr Dermatol* 2013;30:112–16.
87. Kettelhut BV, Metcalfe OD. Pediatric mastocytosis. *J Invest Dermatol* 1991;96:S15–18.
88. Stein DH. Mastocytosis: a review. *Pediatr Dermatol* 1986;3:365–75.
89. Boyano T, Carrascosa T, Val J, et al. Urticaria pigmentosa in monozygotic twins. *Arch Dermatol* 1990;126:1375–6.
90. Ahmad N, Evans P, Lloyd-Thomas AR. Anesthesia in children with mastocytosis – a case based review. *Pediatr Anesth* 2009;19:97–107.
91. Caplan RM. The natural course of urticaria pigmentosa. *Arch Dermatol* 1963;87:146–57.
92. Neri I, Guareschi E, Guerrini V, et al. Familial telangiectasia macularis eruptiva perstans. *Pediatr Dermatol* 2005;22:488–9.
93. Lucaya J, Perez-Candela V, Celestina A, et al. Mastocytosis with skeletal and gastrointestinal involvement in infancy. Two case reports and a review of the literature. *Radiology* 1979;131:363–6.
94. Kettelhut BV, Metcalfe DD. Plasma histamine concentration in the evaluation of pediatric mastocytosis. *J Pediatr* 1987;111:419–21.
95. Amon U, Hartmann K, Horny H-P, et al. Mastocytosis – an update. *J der Dtsch Dermatol Ges* 2010;8:695–712.
96. Alvarez-Twose I, Vañó-Galván S, Sánchez-Muñoz L, et al. Increased serum baseline tryptase levels and extensive skin involvement are predictors for the severity of mast cell activation episodes in children with mastocytosis. *Allergy* 2012;67:813–21.
97. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25(7):603–25.
98. Shah PY, Sharma V, Worobec AS, et al. Congenital bullous mastocytosis with myeloproliferative disorder and c-kit mutation. *J Am Acad Dermatol* 1998;39:119–21.
99. Garriga MM, Friedman MM, Metcalfe DD. A survey of the number and distribution of mast cells in the skin of patients with mast cell disorders. *J Allergy Clin Immunol* 1988;82(3, pt 1):425–32.
100. Kettelhut BV, Metcalfe DD. Pediatric mastocytosis. *Ann Allergy* 1994;73:197–202.
101. Mauleón-Fernández C, Sáez-de-Ocariz M, Rodríguez-Jurado R, et al. Nodular scabies mimicking urticaria pigmentosa in an infant. *Clin Exp Dermatol* 2005;30:595–6.
102. Azana MJ, Torrelo A, Mediero IG, et al. Urticaria pigmentosa: A review of 67 pediatric cases. *Pediatr Dermatol* 1994;11:102–6.
103. Murphy M, Walsh D, Drumm B, et al. Bullous mastocytosis: a fatal outcome. *Pediatr Dermatol* 1999;16:452–5.
104. Kettelhut BV, Berkebile C, Bradley D, et al. A double-blind placebo controlled, crossover trial of ketotifen versus hydroxyzine in the treatment of pediatric mastocytosis. *J Allergy Clin Immunol* 1989;83:866–70.
105. Horan RF, Sheffer AL, Austen KF. Cromolyn sodium in the management of systemic mastocytosis. *J Allergy Clin Immunol* 1990;85:852–5.
106. Turk J, Oates JA, Roberts LJ. Intervention with epinephrine in hypotension associated with mastocytosis. *J Allergy Clin Immunol* 1983;71:189–92.
107. Smith ML, Orton PW, Chu H, et al. Phototherapy of dominant, diffuse, cutaneous mastocytosis. *Pediatr Dermatol* 1990;7:251–5.
108. Kan AE, Rogers M. Juvenile hyaline fibromatosis: an expanded clinicopathologic spectrum. *Pediatr Dermatol* 1989;6:68–75.
109. Mendonça JA, Marini R, Bossolan-Schincariol N, et al. Ultrasound findings in infantile systemic hyalinosis. *Rheumatol Int* 2011;31(10):1393–5.
110. Fayad MN, Yacoub A, Salman S, et al. Juvenile hyaline fibromatosis: Two new patients and review of the literature. *Am J Med Genet* 1987;26:123–31.
111. Dowling O, Difeo A, Ramirez MC, et al. Mutations in capillary morphogenesis gene-2 result in the allelic disorders juvenile hyaline fibromatosis and infantile systemic hyalinosis. *Am J Hum Genet* 2003;73:957–66.
112. Hanks S, Adams S, Douglas J, et al. Mutations in the gene encoding capillary morphogenesis protein 2 cause juvenile hyaline fibromatosis and infantile systemic hyalinosis. *Am J Hum Genet* 2003;73:791–800.
113. Tanaka K, Ebihara T, Kusubata M, et al. Abnormal collagen deposition in fibromas from patient with juvenile hyaline fibromatosis. *J Dermatol Sci* 2009;55:197–200.
114. Winchester P, Grossman H, Lim WN, et al. A new acid mucopolysaccharidosis with skeletal deformities simulating rheumatoid arthritis. *Am J Roentgenol* 1969;106:121–8.
115. Farber S. A lipid metabolic disorder – disseminated ‘lipogranulomatosis’ a syndrome with similarity to, and important difference from, Niemann-Pick and Hand-Schüller-Christian diseases. *Am J Dis Child* 1952;84:499–500.
116. Abenzo P, Sibley RK. Farber’s disease: a fine structural study. *Ultrastruct Pathol* 1987;11:397–403.
117. Vormoor J, Ehler K, Groll AH, et al. Successful hematopoietic stem cell transplantation in Farber disease. *J Pediatr* 2004;144:132–4.
118. Haraoka G, Muraoka M, Yoshioka N, et al. First case of surgical treatment of Farber’s disease. *Ann Plast Surg* 1997;39:405–10.
119. Fensome AH, Benson PF, Neville BR, et al. Prenatal diagnosis of Farber’s disease. *Lancet* 1979;2:990–2.
120. Muenzer J. Mucopolysaccharidoses. *Adv Pediatr* 1986;33:269–302.
121. Matsuyama T, Sly WS, Kondo N, et al. Treatment of MPS VII (Sly syndrome) by allogeneic BMT in a female with homozygous A619V mutation. *Bone Marrow Transplant* 1998;21:629–34.
122. Hirschhorn K, Willner J. Disorders of metabolism. In: Spitz JL, editor. *Genodermatoses: a full-color clinical guide to genetic skin disorders*. Baltimore: Williams & Wilkins; 1996. p. 266–7.
123. Schiro JA, Mallory SB, Demmer L, et al. Grouped papules in Hurler-Scheie syndrome. *J Am Acad Dermatol* 1996;35:868–70.
124. Maize J, Metcalf J. Metabolic diseases of the skin. In: Elder D, Elenitsas R, Jaworsky C, et al, editors. *Lever’s histopathology of the skin*. 8th ed. Philadelphia: Lippincott-Raven; 1997. p. 393.
125. Vellodi A, Young EP, Cooper A, et al. Bone marrow transplantation for mucopolysaccharidosis type I: experience of two British centres. *Arch Dis Child* 1997;76:92–9.
126. Kakkis ED, Muenzer J, Tiller GE, et al. Enzyme-replacement therapy in mucopolysaccharidosis I. *New Engl J Med* 2001;344:182–8.

127. Wraith JE, Clarke LA, Beck M, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). *J Pediatr* 2004;144:581–8.
128. Wraith JE, Hopwood JJ, Fuller M, et al. Laronidase treatment of mucopolysaccharidosis I. *BioDrugs* 2005;19:1–7.
129. Fensom AH, Benson PF. Recent advances in the prenatal diagnosis of the mucopolysaccharidoses. *Prenat Diagn* 1994;14:1–12.
130. Ting J, Hochwald O, Au N, et al. Blueberry muffin rash and thrombocytopenia in a newborn with mucopolipidosis type II (I-cell disease) masquerading as congenital infections. *Mol Genet Metab* 2011;104(4):708–9.
131. Leroy JG, Martin JJ. Mucopolipidosis II (I-cell disease): Present status of knowledge. *Birth Defects Orig Artic Ser* 1975;11:283–93.
132. Yuksel A, Kayserili H, Gungor F. Short femurs detected at 25 and 31 weeks of gestation diagnosed as Leroy I-cell disease in the postnatal period: a report of two cases. *Fetal Diagn Ther* 2007;22:198–202.
133. Terashima Y, Tsuda K, Isomura S, et al. I-cell disease: Report of three cases. *Am J Dis Child* 1975;129:1083–90.
134. McDowell G, Gahl WA. Inherited disorders of glycoprotein synthesis: Cell biological insights. *Proc Soc Exp Biol Med* 1997;215:145–57.
135. Leroy JG, Demars RI. Mutant enzymatic and cytological phenotypes in cultured human fibroblasts. *Science* 1967;157:804–6.
136. von Figura K, Haslik A, Pohlmann R, et al. Mutations affecting transport and stability of lysosomal enzymes. *Enzyme* 1987;38:144–53.
137. Grewal S, Shapiro E, Braunlin E, et al. Continued neurocognitive development and prevention of cardiopulmonary complications after successful BMT for I-cell disease: a long-term follow-up report. *Bone Marrow Transplant* 2003;32:957–60.
138. Aula P, Rapola J, Autio S, et al. Prenatal diagnosis and fetal pathology of I-cell disease (mucopolipidosis type II). *J Pediatr* 1975;87:221–6.
139. Carey WF, Jaunzems A, Richardson M, et al. Prenatal diagnosis of mucopolipidosis II – electron microscopy and biochemical evaluation. *Prenat Diagn* 1999;19:252–6.
140. Xu W, Wang L, Zhang L, et al. Otolaryngological manifestations and genetic characteristics of lipoid proteinosis. *Ann Otol Rhinol Laryngol* 2010;119:767–71.
141. Al-Faky YH, Bosley TM, Al-Turki T, et al. Prominent corneal nerves: a novel sign of lipoid proteinosis. *Br J Ophthalmol* 2012;96(7):935–40.
142. Hamada T, McLean WH, Ramsay M, et al. Lipoid proteinosis maps to 1q21 and is caused by mutations in the extracellular matrix protein 1 gene (ECM1). *Hum Mol Genet* 2002;11:833–40.
143. Kroukamp G, Lehmann K. Treatment of laryngeal lipoid proteinosis using CO2 laser. *S Afr Med J* 2007;97(2):92.
144. Gruber F, Manestar D, Stasic A, et al. Treatment of lipoid proteinosis with etretinate. *Acta Dermatol Venereol* 1996;76:154–5.
145. Lum D. Cutaneous mucinosis of infancy. *Arch Dermatol* 1980;116:198–200.
146. Podda M, Rongioletti F, Greiner D, et al. Cutaneous mucinosis of infancy: is it a real entity or the paediatric form of lichen myxoedematosus (papular mucinosis)? *Br J Dermatol* 2001;144(3):590–3.

Selected Hereditary Diseases

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Approach to the child with a genetic skin condition

To effectively care for an affected newborn and provide information for anxious parents, an organized diagnostic approach is essential. The physical exam requires special attention to ectodermal involvement by assessing the hair, teeth, nails, palms and soles of the feet. Moving beyond the skin, a child should be examined for dysmorphic features, associated major or minor congenital anomalies and accompanying illness. Results of a newborn hearing screen and pediatric ophthalmology exam are often valuable. Finally, a detailed family history including ethnic background and miscarriage history is beneficial. After gathering clinical information, superb resources are available online to consider diagnostic possibilities. One example is Online Mendelian Inheritance in Man (OMIM; <http://www.ncbi.nlm.nih.gov/omim>).

OMIM is maintained by the National Center for Biotechnology Information (NCBI) and can be searched using a list of the clinical features in an affected patient. Each disorder is assigned a number based on broad categories such as inheritance pattern. ‘GeneTests’ (<http://www.ncbi.nlm.nih.gov/sites/GeneTests>) and a separate database, ‘GeneReviews’¹ offers a frequently updated list of internationally available DNA-based genetic tests and concise, yet comprehensive overviews of selected disorders. For effective coordination of testing and advising the patient about the complexities of genetic testing and reproductive options, the GeneTests site provides a database of genetics services that is searchable by country and province or state. Increasingly, individual mutations that cause familial genetic disorders are recognized to affect important regulatory pathways. This chapter highlights pathways that are particularly important to growth and development of the skin.

Disorders of the RAS-MAPK pathway (RASopathies)

Several genetic skin disorders are caused by mutations in genes in the RAS-MAPK signaling pathway (Fig. 29.1) and have been coined the ‘RASopathies’.² The RASopathies include neurofibromatosis-1 (NF-1), NF-like syndrome (Legius syndrome), Noonan syndrome, Noonan with multiple lentigines (formerly LEOPARD syndrome), cardiofaciocutaneous syndrome, Costello syndrome, capillary malformation–arteriovenous malformation (see Chapter 22), and hereditary gingival fibromatosis (Table 29.1). Neurofibromatosis and Legius syndrome are also discussed in Chapter 24.

NEUROFIBROMATOSIS TYPE 1

Neurofibromatosis 1 (NF-1, MIM #162200) is a multisystem disorder characterized by age-related abnormalities of tissue

proliferation. NF-1 is one of the most common autosomal dominant genetic conditions with an incidence of approximately 1 in 3000 individuals.^{3,4} Consensus criteria for the diagnosis of NF-1 were established at the 1988 NIH conference to be used as a guideline for clinical diagnosis (Box 29.1).⁵ In 95% of affected individuals, a diagnosis can be made by age 11 through the use of clinical evaluation alone.⁶ However, NF-1 can be a difficult condition to diagnose in some infants due to the high incidence of sporadic mutations, variability of clinical expression, and age-related penetrance of individual clinical manifestations. Hence, anticipatory guidance counseling should be provided in both established and suspected cases of NF-1.

Cutaneous findings

Café-au-lait macules (CALM) are light to dark brown sharply defined oval macules and patches which can occur on almost any skin surface (Fig. 29.2A). Infants with ≥ 6 café-au-lait macules >5 mm in diameter that are not confined to a single segmental region, should be evaluated and managed as though they have NF-1, even without other signs of NF-1, because of the high likelihood that they will develop other diagnostic signs with time. At puberty, if other features are lacking, the approach and diagnosis can be reconsidered.

Intertriginous freckling of the axillary and inguinal regions may occasionally be present in infancy, but most often present between 2–10 years of age (Fig. 29.2B). Although freckling on the neck and trunk is common in NF-1, it is not accepted as a diagnostic criterion.

Peripheral neurofibromas are infrequent in early childhood NF-1, occurring in only 14% of children less than 10 years of age.⁶ Often the first sign of dermal neurofibromas are 3–6 mm, light blue, minimally raised papules which are most easily detected with side lighting. It has been suggested that a subset of children with large deletions of the NF-1 gene typically present with multiple neurofibromas in early childhood.⁷

Plexiform neurofibromas may be apparent at birth or soon thereafter; however because they are often internal, may be difficult to detect. They occur in at least 25% of affected individuals (Fig. 29.2C). Most have overlying hyperpigmentation; some – but not all – have increased vascularity resembling a vascular anomaly or hypertrichosis resembling a congenital melanocytic nevus. Plexiform neurofibromas may grow rapidly and interdigitate with and surround normal structures. Radiologic imaging and neurosurgical consultation should be considered if lesions are extensive or close to major nerve bundles.

Extracutaneous findings

Optic gliomas are astrocytomas arising anywhere along the optic pathway. These lesions tend to arise in infancy or early childhood. Half of the tumors are symptomatic, causing loss of

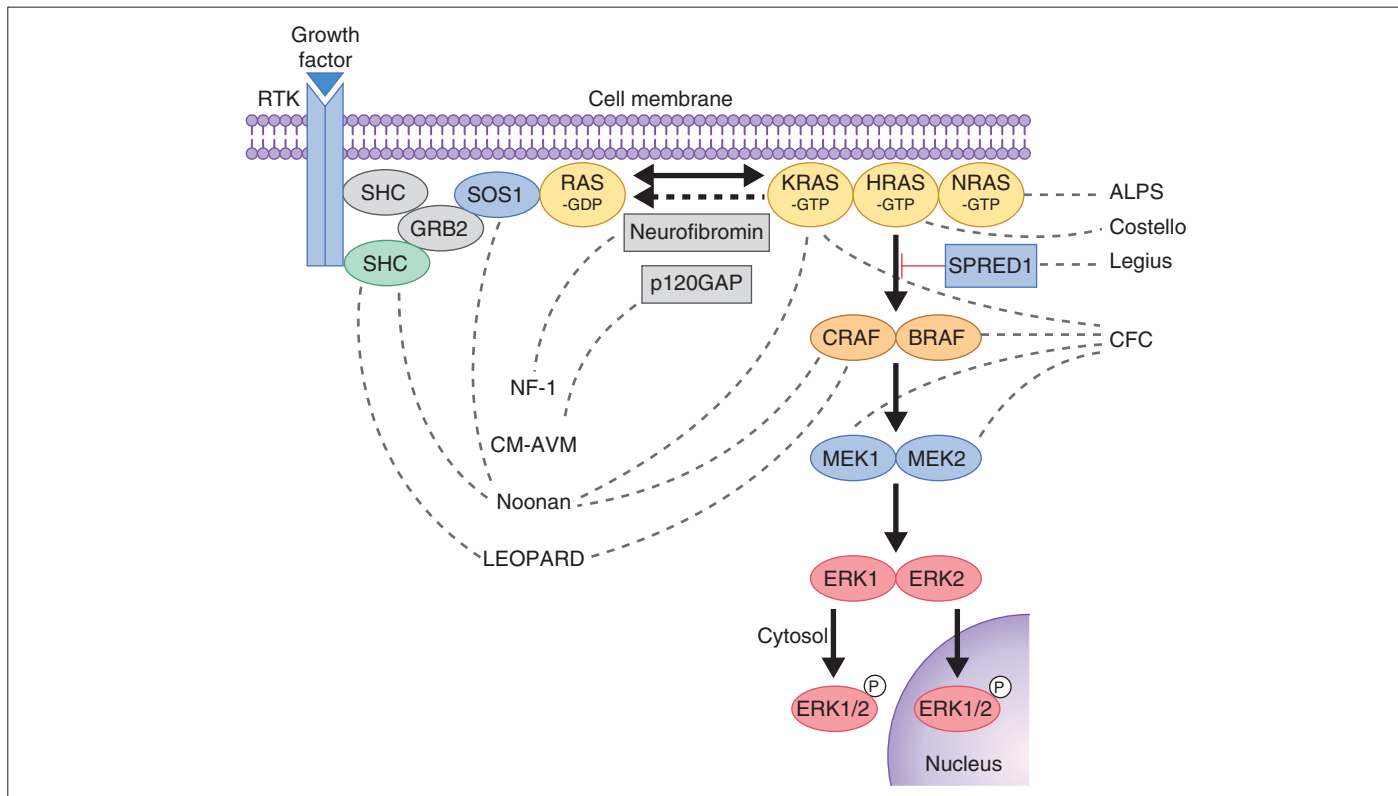


Figure 29.1 The RAS/mitogen-activated protein kinase (MAPK) signaling pathway is important in cell proliferation, differentiation, motility, apoptosis and senescence. Disorders resulting from mutations in the genes of the RAS/MAPK have been coined the RASopathies and include Noonan, multiple lentigines syndrome, gingival fibromatosis 1, neurofibromatosis 1, capillary malformation-arteriovenous malformation, Costello, autoimmune lymphoproliferative (ALPS), cardiofaciocutaneous and Legius syndromes. (Adapted from *Curr Opin Genet Dev* 2009; 19(3):230–236. Published online 2009 May 19. doi: 10.1016/j.gde.2009.04.001.)

visual acuity, decreased field of vision, proptosis, or interference with the hypothalamopituitary axis. Symptomatic optic gliomas are often diagnosed by 6 years of age.

Lisch nodules are pigmented iris hamartomas that rarely present in infants, and only 20% of individuals under 5 years of age with NF-1 have Lisch nodules. They are best seen on slit-lamp examination and do not result in functional disability. Congenital glaucoma occurs in less than 0.05% of individuals with NF-1 and may present with an ipsilateral neurofibroma of the eyelid.

Relatively short stature and large head size are frequent findings and more common than the more diagnostic skeletal changes, pseudoarthrosis and sphenoid wing dysplasia. Pseudoarthrosis represents the failure of union after fracture. It is always unilateral and most commonly presents in the tibia as anterolateral bowing. Ultimately, pseudoarthrosis can progress to severe deformity. Sphenoid wing dysplasia is a unilateral defect of the orbit present in approximately 5% of individuals with NF-1 and results in a change in orbit structure. Approximately half of those cases with sphenoid wing dysplasia develop an ipsilateral temporal–orbital plexiform neurofibroma, and half of individuals presenting with a temporal–orbital tumor also have an underlying plexiform neurofibroma. Learning disabilities occur in approximately 50% of children with NF-1. The main learning difficulties include reading, deficits in perceptual skills (visuospatial) and executive functioning. Attention issues are also common.⁸

BOX 29.1 NIH CONSENSUS CRITERIA FOR NEUROFIBROMATOSIS 1

- ≥ 6 café-au-lait macules >5 mm in greatest diameter in prepubertal individuals or >15 mm in greatest diameter after puberty
- ≥ 2 neurofibromas of any type, or ≥ 1 plexiform neurofibromas
- Axillary/inguinal freckling (Crowe's sign)
- Tumor of the optic nerve pathway (optic glioma)
- ≥ 2 Lisch nodules (iris hamartomas)
- Distinctive osseous changes (e.g., sphenoid wing dysplasia or pseudoarthrosis)
- First-degree relative with NF-1

Etiology and pathogenesis

NF-1 is due to an autosomal dominant mutation localized to chromosome 17 that results in defects in neurofibromin, a tumor suppressor protein that stimulates hydrolysis of guanosine triphosphate (GTP) bound to *ras*.⁹

Differential diagnosis and diagnosis

Café-au-lait macules may be found in many other conditions, including segmental pigmentary disorder and McCune–Albright syndrome (see Chapter 24). Additional differential diagnoses for multiple café-au-lait macules are shown in Box 29.2. Genetic testing for NF-1 is available from several commercial and research laboratories (see: www.genetests.org, for

TABLE 29.1 Comparison of the clinical features of the RASopathies

	NF-1	Cardiofacio-cutaneous syndrome	Costello syndrome	Noonan syndrome	Multiple lentigines syndrome	Capillary malformation-arteriovenous malformation
Gene	NF1	BRAF, MEK1, MEK2, KRAS	HRAS	PTPN11, SOS1, KRAS, NRAS, RAF1, SHOC2, CBL and BRAF	PTPN11, RAF, BRAF	RASA1
Dermatologic features	Café-au-lait macules Intertriginous freckling Neurofibromas Plexiform neurofibroma	Ulerythema ophryogenes Keratosis pilaris Melanocytic nevi Infantile hemangiomas	Papillomata of the nose and perianal region Palmoplantar hyperkeratosis Redundant skin on the hands and feet Acanthosis nigricans	Congenital lymphedema Café-au-lait macules Keratosis pilaris (most common with SOS1 mutations)	Lentigines Café noir patches	Capillary malformations Arteriovenous malformations of the brain, spine, skin, muscle and bone
Cardiac features	Uncommon	Pulmonic stenosis Hypertrophic cardiomyopathy	Pulmonic stenosis Hypertrophic cardiomyopathy	Pulmonic stenosis Hypertrophic cardiomyopathy	EKG abnormalities Pulmonic stenosis Hypertrophic cardiomyopathy	Rare
Tumor predisposition	Yes: Optic glioma Hematologic malignancies Meningioma and other brain cancers Malignant peripheral nerve sheath tumor Pheochromocytoma Lisch nodules Learning disability Pseudoarthrosis Macrocephaly Sphenoid wing dysplasia Renal artery stenosis Hypertension	Rare: Possible risk for ALL and lymphoma	Yes: Malignant solid tumors (rhabdomyosarcoma, neuroblastoma, transitional cell carcinoma of the bladder)	Rare: Hematologic malignancies	Rare: Hematologic malignancies	Rare: Possible increased risk for neural tumors
Other		Failure to thrive (severe) Developmental delay	Failure to thrive (mild) Developmental delay Sociable, outgoing personality	Low posterior hairline Webbed neck Pectus excavatum Bleeding tendency Short stature	Ocular hypertelorism Sensorineural hearing loss Short stature	Risk for intracranial and spinal arteriovenous malformation Parkes-Weber syndrome



Figure 29.2 (A) Multiple café-au-lait macules in an infant with neurofibromatosis. (B) Axillary freckling and multiple café-au-lait macules. (C) Plexiform neurofibroma of the hip of a 2-year old boy. Note the ill-defined borders and dark brown color in comparison to the sharp borders and light brown color of the café-au-lait macule on the thigh. (Courtesy of Dr V.P. Sybert.)

BOX 29.2 DIFFERENTIAL DIAGNOSIS FOR MULTIPLE CAFÉ-AU-LAIT MACULES

- Legius syndrome
- Neurofibromatosis type 2
- Schwannomatosis
- Noonan syndrome
- Noonan syndrome with multiple lentigines (LEOPARD syndrome)
- Multiple endocrine neoplasia 2B
- Bannayan–Riley–Ruvalcaba syndrome
- Piebald trait

BOX 29.3 CARE PLAN: EXTRACUTANEOUS MANIFESTATIONS OF NEUROFIBROMATOSIS 1

- Routine history and physical examination by a pediatrician
- Yearly blood pressure monitoring
- Baseline and annual ophthalmologic examination
- Routine neurologic and developmental evaluation
- Regular head circumference monitoring
- Genetic counseling with discussion of genetic testing
- Imaging based on neurologic signs and symptoms

specific information). Decisions regarding whether laboratory-based NF testing is appropriate are best made in conjunction with a geneticist and genetic counselor.

Treatment and care

Patients with neurofibromatosis require age-related anticipatory guidance counseling and regular follow-up with a pediatrician, ophthalmologist and geneticist. Additional specialists can be included, based on symptoms or complications and may include orthopedics, neurology, dermatology, neuropsychology, and neurosurgery (Box 29.3). Ophthalmologists and

neurologists should evaluate for optic nerve pathway tumors and glaucoma. Anterolateral tibial bowing when present require prompt orthopedic evaluation, because the critical time for fracture and poor healing is infancy to early childhood.⁶ Periodic evaluation for scoliosis is also necessary. Regular physical examinations should include careful measurement of blood pressure because of a higher incidence of hypertension secondary to renovascular disease, vasoactive secreting tumors, and coarctation of the aorta.⁶ Head circumference should be monitored because of the risk of hydrocephalus and the occurrence of macrocephaly without hydrocephalus. Careful developmental

assessment is a key part of management, as the risk of neurologic abnormalities and learning disabilities is increased.

Dermal neurofibromas are benign and should only be excised if they are symptomatic or disfiguring. Plexiform neurofibromas require close evaluation. Skin should be palpated carefully as plexiform neurofibromas may remain below the surface. If there are symptoms or neurologic abnormalities on clinical exam, MRI scans should be obtained to determine the extent of plexiform neurofibromas. Serial imaging or volumetric MRI may be necessary to assess potential growth. Pain and/or growth may herald malignant transformation, but this is exceedingly rare in infancy. Neurologic compromise may result from perineural extension, however, and neurology and/or neurosurgery may need to be consulted for plexiform lesions near neurovascular structures (such as the neck, axilla and spinal area).⁶ Orbitotemporal neurofibromas may be better managed by numerous surgical procedures over time; plastic surgery should be involved early for management of these tumors.

LEGIUS SYNDROME

Legius syndrome (MIM #611431) was first recognized in 2007 as an NF-1-like syndrome in families with multiple café-au-lait macules, but negative NF-1 gene testing.¹⁰ The phenotype is milder than NF-1 and seems to lack the propensity for tumor development. The clinical features include a mild NF-like phenotype and 50% of these patients meet diagnostic criteria for NF-1. Of the diagnostic criteria for NF-1 (Box 29.1), the features that have been reported in Legius include >6 CALM >5 mm, intertriginous freckling, positive family history, macrocephaly, short stature and learning disabilities.¹¹ Neurofibromas, plexiform neurofibromas, bone dysplasia and scoliosis have not been associated with Legius syndrome. Legius syndrome is caused by loss of function (LOF) mutations in the *SPRED1* gene.¹⁰ Like neurofibromin, *SPRED1* is a negative regulator of the RAS-MAPK pathway (Fig. 29.1).¹¹

NOONAN SYNDROME

Noonan syndrome (MIM #163950) is an autosomal dominant multisystem disorder characterized by congenital lymphedema, broad or webbed neck, low posterior hairline, short stature, and cardiac malformations (Box 29.4).

Cutaneous findings

The neonate with Noonan syndrome is unlikely to have skin manifestations other than nuchal webbing and peripheral lymphedema that suggest the diagnosis. Keratosis pilaris atrophicans faciei (ulerythema ophryogenes), characterized by horny, whitish, hemispherical, or acuminate papules at the opening of pilosebaceous follicles, is generally noted in older children, but may manifest in the external third of the eyebrows by a few months after birth. Some children with Noonan syndrome have multiple CALM and/or lentigines.

Extracutaneous findings

Neonates have a characteristic facial appearance consisting of a tall forehead, low posterior hairline, hypertelorism, downslanting palpebral fissures, epicanthal folds, short and broad, depressed nasal root, deeply grooved philtrum and micrognathia. The chest shape is unique with superior pectus carinatum and inferior pectus excavatum. Feeding difficulties,

BOX 29.4 CLINICAL FEATURES: NOONAN SYNDROME

DERMATOLOGIC ASSOCIATIONS

- Webbed neck
- Cutis verticis gyrata
- Ulerythema ophryogenes
- Koilonychia
- Thick, curly and wooly hair
- Prominent fetal finger pads

EXTRACUTANEOUS MANIFESTATIONS

- Short stature
- Craniofacial:
 - Ptosis
 - Downslanting palpebral fissures
 - High palate
- Cardiac pulmonic stenosis
- Cryptorchidism

gastroesophageal reflux and failure to thrive are frequent problems in infancy. Unilateral or bilateral cryptorchidism are common in boys. Infants are at risk for transient monocytosis, thrombocytopenia and myeloproliferative disorder.¹² Coagulation defects occur in approximately one-third of patients with Noonan syndrome and may present with easy bruising or prolonged bleeding times. There is a slightly increased risk of hematologic malignancy (most commonly juvenile myelomonocytic leukemia, JMML) compared with the general population. The classic congenital heart defect in Noonan syndrome is pulmonic stenosis.

Etiology and pathogenesis

The incidence of Noonan syndrome is approximately 1 in 1000–2500 live births.¹³ Noonan syndrome may be caused by a mutation in one of several genes in the RAS-MAPK signaling pathway, including *PTPN11*, *SOS1*, *KRAS*, *NRAS*, *RAF1*, *SHOC2*, *CBL*, and *BRAF*.¹⁴ *PTPN11* and *CBL* mutations have a higher rate of bleeding diathesis and JMML. Patients with *SOS1* mutations have a lower rate of intellectual disability. *SHOC2* mutations have been associated with a Noonan phenotype with loose anagen hair.¹⁵ *PTPN11* mutations are also the genetic basis of Noonan with multiple lentigines (formerly known as LEOPARD syndrome;¹⁶ see Chapter 24).

Differential diagnosis

In the neonatal period, the RASopathies can be very difficult to distinguish as they share the features of congenital heart defects, severe feeding difficulties and developmental delay.¹⁷ Later in infancy, facial and ectodermal features become more distinct for each of the RASopathies. Cardiofaciocutaneous syndrome and Costello syndrome are described in more detail below.

Treatment and care

Patients with Noonan syndrome should be monitored for growth deficiency and developmental delay. Electrocardiogram and echocardiography should be performed at the time of diagnosis and repeated as indicated based on findings. A renal ultrasound is recommended at diagnosis. Coagulopathy work-up should be performed if the patient has a history of either easy bruising or prolonged bleeding.¹⁴

TABLE
29.2

Dermatologic features found in cardiofaciocutaneous syndrome compared with Costello syndrome

	Percentage of cases	
	Cardiofaciocutaneous	Costello
Curly hair	93.4%	95.7%
Eyebrow density	90.0% sparse	47.8% thick
Keratosis pilaris	80.3%	32.6%
Infantile hemangioma	26.2%	10.9%
Papillomas	4.9%	71.7%
More than 50 nevi	23.0%	4.0%
Palmoplantar keratoderma	36.1%	76.1%

(Adapted from Siegel DH, Mann JA, Krol AL, Rauen KA. Dermatological phenotype in Costello syndrome: consequences of Ras dysregulation in development. *Br J Dermatol* 2012; 166(3):601–607.)

CARDIOFACIOCUTANEOUS SYNDROME

Cardiofaciocutaneous (CFC) syndrome (MIM #115150) is characterized by short stature, congenital heart defects, intellectual disability, ectodermal abnormalities and a characteristic coarse facial appearance (Table 29.2). Numerous cutaneous findings have been reported in CFC. In 2010, Siegel and colleagues¹⁸ evaluated the cutaneous manifestations in 61 mutation-positive individuals with CFC syndrome. All had dermatologic findings. One of the striking features identified in this study was a high number of melanocytic nevi. In the study, 23% of participants had over 50 nevi and 36% of those patients reported over 100 nevi. The amount of nevi increased with age and were not a prominent feature in infancy. Keratosis pilaris and ulerythema ophryogenes were very common and affected the majority of individuals in childhood and adolescence (Fig. 29.3). Infantile hemangiomas occurred at a greater frequency when compared with the general population. Additional features in CFC include macrocephaly, characteristic facial appearance, growth retardation, cardiac defects, neurologic impairment, gastrointestinal dysfunction, and ocular abnormalities.

CFC syndrome is caused by mutations in *BRAF*, *MEK1* or *MEK2*.^{19,20} These mutations were discovered in part because of the similarity of the phenotypic features of Noonan and Costello syndromes, both of which were known to have mutations involving the RAS-MAPK pathway. Given insights into genetics and pathogenesis, it is not surprising that the main differential diagnoses for CFC syndrome include Noonan and Costello syndromes.

COSTELLO SYNDROME

Costello syndrome (CS) (MIM #218040) is a rare, autosomal dominant, multiple congenital anomaly syndrome associated with failure to thrive, developmental delay, and an increased risk of malignancy.²¹ The features of Costello syndrome in the neonatal and infantile period include macrosomia, severe feeding problems, developmental delay, coarse facial features, gingival hyperplasia, osteopenia, hypertrophic cardiomyopathy and atrial arrhythmias.²² The most common malignancies include rhabdomyosarcoma, neuroblastoma and transitional cell cancer of the bladder. CS is caused by mutations in the *HRAS* gene, at 11p15.5, leading to constitutive activation of the RAS-MAPK pathway.²¹ The cutaneous findings include curly



Figure 29.3 Cardiofaciocutaneous syndrome in an infant with a confirmed *BRAF* mutation. The sparse curly hair and eyebrows and characteristic facial features are evident. (Courtesy of Brenda Conger, CFC International.)

hair, papillomas on the perinasal, perioral and perianal skin, palmoplantar keratoderma, unusual body odor and heat intolerance. The skin on hands is loose and redundant (Fig. 29.4A). Acanthosis nigricans has been reported in 37% of the cases (Fig. 29.4B).²³ In the neonatal period, it can be difficult to distinguish Costello, CFC and Noonan syndromes, as all three conditions can manifest with neonatal macrosomia, coarse facial features, failure to thrive and developmental delay.¹⁷

CAPILLARY MALFORMATION-ARTERIOVENOUS MALFORMATION (CM-AVM) (MIM #608354)

CM-AVM is an autosomal dominant disorder characterized by multiple, small, oval capillary malformations on the face, body and limbs, which are associated with arteriovenous malformations in about 30% of cases. The AVMs can occur in the brain, spine, muscle or skin. CM-AVM is caused by mutations in the *RASA1* gene.²⁴ See Chapter 22 for a more in-depth discussion about this condition.

NEUROFIBROMATOSIS TYPE 2

Neurofibromatosis type 2 (NF-2) (MIM #101000) is an autosomal dominant condition characterized by a high burden of schwannoma and meningioma tumor development.

Presentation in infancy is rare, although cutaneous schwannomas have been reported.²⁵ Cutaneous features which may be present in infancy or early childhood include CALM and cutaneous schwannomas (Fig. 29.5). The age range at the onset of NF-2-related symptoms is 5–55 years. The initial symptoms that lead to the diagnosis include hearing loss, visual disturbance, and enlarging subcutaneous mass. The incidence of NF-2 is difficult to predict due to a high rate of mosaicism, but is estimated at about 1:25 000.²⁶ NF-2 is caused by mutations in the merlin (also called schwannomin) tumor suppressor gene on chromosome 22q12.²⁷ The differential diagnosis for NF-2 includes NF-1 and schwannomatosis.

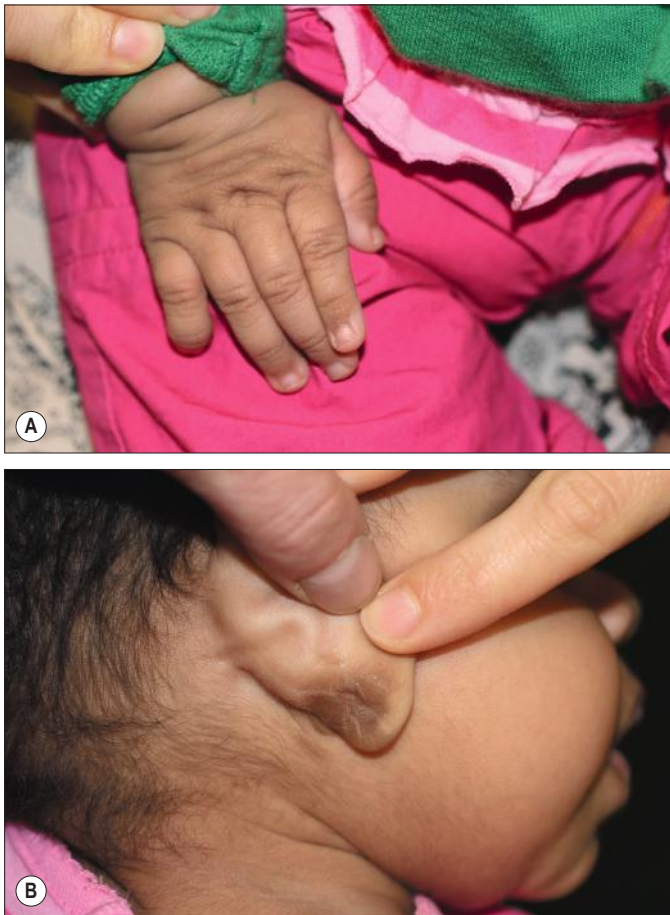


Figure 29.4 (A) The characteristic loose, redundant skin of the hand and (B) acanthosis nigricans behind the ear lobe in an individual with Costello syndrome.



Figure 29.5 Cutaneous schwannomas presenting as multilobulated, pink to flesh colored rubbery plaques in an infant. (Courtesy of Dr S. Galbraith.)

Disorders of the PI3K-AKT/mTOR pathway and overgrowth syndromes

Overgrowth syndromes and human cancer share disruption of similar critical regulatory pathways (Table 29.3). Intensive

cancer research, therefore, has improved our understanding of these rare but important disorders. The phosphatidylinositol 3-kinase (PI3K)-AKT pathway, in particular, critically guides cell growth and metabolism (Fig. 29.6). The PI3K enzymes are a family of highly conserved enzymes that regulate cell growth, migration and survival and disruption in the embryonic period typically impacts vascular, limb or brain development.²⁹ Mutations cause recognizable patterns of increased cell number, hypertrophy, increased interstitium, or a combination of these.³⁴ Typical neonatal clues of an overgrowth syndrome are abnormally increased body length, macrosomia, and macrocephaly, dysregulated growth of a body part or asymmetry (Fig. 29.7). Almost all overgrowth syndromes are associated with neoplasms, especially solid tumors.

PI3K-AKT activity is considered so essential that disruptive germline mutations are often presumed fatal. For example, an activating PI3K pathway mutation appears only in the mosaic form. In addition to impacting embryonic development, the PI3K-AKT pathway participates in normal cellular function by regulating glucose metabolism and apoptosis.³⁵ Therefore, mutations affecting this pathway may cause congenital anomalies as well as ongoing complications. Improved understanding of the PI3K pathway, especially by revealing therapeutic targets for inhibitory drugs like rapamycin, gives hope for future trials and treatment.³⁶

TUBEROUS SCLEROSIS

Tuberous sclerosis (TSC, MIM #191100) is a multisystem disorder characterized by tumors and hamartomas affecting the skin, brain, heart, kidneys and lungs, often in association with seizures and developmental delay (Box 29.5). TSC is discussed in further detail in Chapter 23.

Cutaneous findings

There is a very high prevalence of cutaneous findings in TSC.³⁷ Hypomelanotic macules are usually present at birth or appear within the first few months of life and ultimately are present in approximately 90% of TSC patients. Classically, they present as an 'ash leaf macule,' an oval area with reduction in pigment (Fig. 29.8A). These areas can also be irregular in outline and shape, or very small and guttate (confetti-like) (Fig. 29.8B). In fair-skinned infants, a Wood's lamp examination may be necessary for detection. They can also occur on the scalp, with lightening of the hair within the patch. A single, hypopigmented macule in an infant, without other features of TSC, should not cause concern,³⁸ but multiple lesions (≥ 3) should lead to further investigation.

Classic facial angiofibromas typically appear after 4 years of age, however fibrous plaques resembling coalescence of angiofibromas may be present over the scalp, face, or neck at birth or appear shortly thereafter, as firm slightly raised patches or plaques that are commonly erythematous (Fig. 29.8C). Shagreen patches – firm, palpable thickened dermal plaques – can occur in the lumbar region as a roughened area of erythematous skin with a rubbery consistency or develop in other areas of the torso (Fig. 29.8D). They range in size from a few millimeters to 15 cm in diameter, and generally appear by adolescence but are infrequent in young infants. Periungual fibromas are similarly uncommon in the first decade. Gingival fibromas are a less common feature, but occasionally develop in young children (Fig. 29.8E).

TABLE 29.3 Overgrowth syndromes and associated clinical features

Syndrome	Causative mutation	Cutaneous features	Extracutaneous features	Associated malignancy
Tuberous sclerosis	<i>TSC1, TSC2</i>	Hypomelanotic macules, angiofibromas, forehead plaques, shagreen patches, periungual fibromas	Seizures, infantile spasms, intellectual disability. Renal cysts and angiomyolipomas, cardiac rhabdomyomas	Malignant angiomyolipoma, renal cell cancer; subependymal giant cell astrocytoma (SEGA)
Proteus	Mosaic <i>AKT1</i>	Cerebriform connective tissue nevi (CCTN), epidermal nevi, vascular malformations, soft subcutaneous masses, patchy dermal hypoplasia, macrodactyly and lipomas	Disproportionate, relentless segmental overgrowth of body parts; skeletal asymmetry, lung cysts, thromboembolism, eye problems, ovarian cysts, epididymal cysts. Overgrowth generally after neonatal period	Mostly benign tumors
Hemihyperplasia-multiple lipomatosis (HH-ML)	Unknown	Superficial capillary vascular malformation, lipomas. Lacks deep vascular malformation and cerebriform connective tissue nevi of Proteus.	Non-distorting overgrowth present at birth	Risk for embryonal malignancies is unknown. Screening for Wilms tumor, adrenal cell carcinoma, hepatoblastoma is recommended ²⁸
Megalencephaly-capillary malformation (MCAP)	Mosaic <i>PIK3CA</i>	Patchy capillary malformations; stretchy skin and joints	Large brain, growth dysregulation, asymmetry, syndactyly, polydactyly, developmental delay, hypotonia, frontal bossing	Mildly increased risk of cancer ²⁴ ; Wilms tumor, leukemia; meningioma reported ²⁹
Mosaic overgrowth with fibroadipose hyperplasia (MOFH)	Activating <i>PIK3CA</i>	Lacks cutaneous features of Proteus	Distorting or non-distorting, segmental overgrowth of muscles, skeleton and fibroadipose tissue that is present at birth	Unknown
SOLAMEN	<i>PTEN</i>	Signs of Cowden: trichilemmoma, acral keratoses, oral papillomas. Lacks cerebriform connective tissue nevi of Proteus	Features of Cowden: macrocephaly, breast and thyroid hamartoma	Breast, thyroid, endometrial
CLOVES	Activating <i>PIK3CA</i>	Vascular anomalies, truncal lipomas, epidermal nevi. May be wrinkled skin on the palms and soles, but not CCTN of Proteus	Non-progressive overgrowth at birth. Overgrown feet, hands; 'sandal gap' toes, severe scoliosis; high vascular-flow masses; phlebectasia; thromboembolism	Unknown
Encephalocraniocutaneous lipomatosis (ECCL)	Unknown, sporadic	Nevus psiloliparus overlying lipomatous overgrowth; angiofibromas, connective tissue nevi ³⁰ cutis aplasia, nodular skin tags ³¹	Proportionate, non-distorting overgrowth at birth. Ocular abnormalities, CNS lipomas, heart defects, lytic bone lesions, hypospadias, cryptorchidism, seizures, jaw osteomas	Mostly benign tumors. Low-grade glioma reported ³⁰
Beckwith–Wiedemann syndrome (BWS)	Imprinting error affecting chromosomal region 11p15.5	Nevus flammeus, distinctive ear creases, posterior helical pits	Abdominal wall defects (omphalocele), placental overgrowth, macrosomia, macroglossia, abnormal kidney, cardiomegaly, hypoglycemia	Tumor risk increased, especially embryonal tumors; requires monitoring
Simpson–Golabi–Behmel syndrome type I	Glypican-3 (<i>GPC3</i>)	Supernumerary nipples, characteristic index finger and nail hypoplasia	Macrosomia, macrocephaly, macroglossia, coarse square-shaped face, abdominal hernias, broad hands, normal intelligence	Risk of embryonal tumors increased; requires monitoring
Sotos syndrome	Nuclear receptor set domain containing protein 1 gene (<i>NSD1</i>)	Frontotemporal sparse hairs, malar flushing	Learning disabilities, distinct facies, macrocephaly, tall stature	Overall cancer risk slightly increased. ³² Age appropriate cancer screening recommended ³³

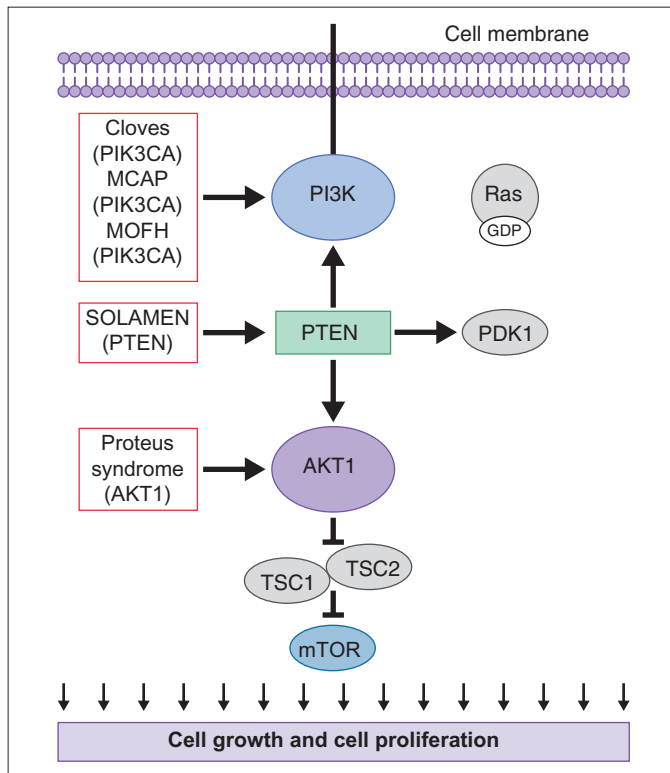


Figure 29.6 PI3K-AKT pathway. Activation of the PI3K-AKT pathway leads to cell growth and proliferation. PI3 Kinase (PI3K) is activated when bound to GTP-bound Ras and certain other ligands. PI3K activates AKT kinases. PTEN antagonizes the activity of PI3K and inhibits the pathway. PTEN also inhibits phosphoinositide-dependent kinase 1 (PDK) and other enzymes to inhibit the pathway. MCAP, megalencephaly-capillary malformation; MOFH, mosaic overgrowth with fibroadipose hyperplasia.



Figure 29.7 Proteus syndrome. Hemihypertrophy and lipomatosis. (Courtesy of Dr V.P. Sybert.)

Extracutaneous findings

Seizures occur in more than 60–80% of patients with TSC.³⁹ Conversely 4–50% of infants with infantile spasms have TSC.^{39,40} TSC patients with early onset of seizures (<2 years of age) or infantile spasms have an elevated risk for intellectual disability. The most common lesions in the brain include tubers, subependymal nodules and subependymal giant-cell astrocytomas (SEGA). Renal cysts, angiomyolipomas, and cardiac rhabdomyomas are findings in newborns and infants that suggest TSC. Cardiac rhabdomyomas are often discovered on routine

BOX 29.5 CLINICAL DIAGNOSTIC CRITERIA FOR TUBEROUS SCLEROSIS

MAJOR FEATURES

- Facial angiofibromas or forehead plaque
- Nontraumatic ungual fibroma
- ≥3 hypomelanotic macules
- Shagreen patch
- Multiple retinal nodular hamartomas
- Cortical tuber^a
- Subependymal nodule
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- Renal angiomyolipoma or pulmonary lymphangiomyomatosis^b

MINOR FEATURES

- Multiple randomly distributed pits in dental enamel
- Hamartomatous rectal polyps
- Bone cysts
- Cerebral white matter radial migration lines^a
- Gingival fibromas
- Nonrenal hamartoma
- Retinal achromic patch
- 'Confetti' skin lesions
- Multiple renal cysts

DIAGNOSTIC REQUIREMENTS

- Definite diagnosis: two major features or one major and two minor features
- Probable diagnosis: one major and one minor feature
- Possible diagnosis: one major or two minor features

^aCerebral cortical dysplasia and cerebral white matter migration tracts count as one feature rather than two when they occur together.

^bOther features of TSC must be present for a definite diagnosis when lymphangiomyomatosis and renal angiomyolipomas are both present.

antenatal ultrasound; 30–50% of infants with TSC have cardiac rhabdomyomas, and 80–90% of infants with these lesions have TSC.⁴¹ They are rarely symptomatic and typically regress spontaneously.⁴² An expert panel at the Tuberous Sclerosis Consensus Conference⁴ recommended a baseline electrocardiogram both at the time of diagnosis and prior to surgery, as cardiac rhabdomyomas can be associated with pre-excitation and arrhythmias on the electrocardiogram.⁴³ Angiomyolipomas are the most common renal manifestation of TSC.

Etiology and pathogenesis

TSC may be caused by an autosomal dominant mutation in the *TSC1* gene (encoding hamartin) or the *TSC2* gene (encoding tuberin). The two proteins form a complex that is involved with the phosphoinositide-3-kinase (PI3K) signaling pathway, which regulates cell growth and proliferation (Fig. 29.6).⁴⁴

Differential diagnosis

The differential diagnosis for the hypopigmented macules seen in the neonatal period includes vitiligo, nevus depigmentosus, nevus anemicus, and piebaldism. A single lesion, or several lesions occurring along the lines of Blaschko suggests the diagnosis of nevoid hypopigmentation rather than TSC (see Chapter 23). Connective tissue nevi may be sporadic and have also been associated with Buschke–Ollendorff or Proteus syndrome. Angiofibromas have been described in MEN1⁴⁵ and Birt–Hogg–Dubé syndrome, and also as an isolated autosomal dominant disorder.



Figure 29.8 Tuberous sclerosis. (A) Ash leaf macules are often present at birth or noted early in infancy. (B) Confetti hypopigmentation typically becomes more common over time. (C) Facial plaque on the left upper cutaneous lip in a 3½-year-old child. (D) Shagreen patch: large shagreen patches may be congenital, whereas smaller ones typically develop over time. (E) Gingival fibromas are a less common feature, but occasionally develop in young children.

Treatment and care

Consensus recommendations for screening and evaluation of TSC were proposed in 1998 and updated in 2000 (Box 29.6).^{43,46} The Scottish Clinical Genetics Service and the UK Tuberous Sclerosis Association have also created clinical guidelines. Neurology and/or neurosurgery should be consulted for management of seizures, brain tumors, and shunting of obstructive hydrocephalus. Ophthalmology should also examine patients to assist in confirming the diagnosis. Renal ultrasound or renal MRI are important to screen angiomyolipomas. This may also help to identify patients with coexisting polycystic kidney

disease due to a contiguous gene deletion syndrome involving the *TSC2* and *PKD1* genes. Echocardiography and electrocardiogram are recommended at diagnosis for confirmation (to detect cardiac rhabdomyomas and arrhythmias) and to screen for aortic aneurysms.⁴⁷

Pulsed dye laser has been recommended for flat erythematous angiofibromas, and both Potassium titanyl phosphate (KTP) laser and carbon dioxide laser are used to treat more elevated lesions, but are rarely indicated in infants.⁴⁸ Fibrous forehead plaques are generally left untreated, but may also be treated with lasers or surgery. Several case reports have recently described the

BOX 29.6 CARE PLAN FOR TUBEROUS SCLEROSIS: TESTING RECOMMENDATIONS IN THE NEONATE OR INFANT AT TIME OF DIAGNOSIS

- Age-appropriate neurologic and developmental assessment
- Dermatologic examination
- Ophthalmic examination
- Neurologic consultation
- Cardiac evaluation (ECG and echocardiogram)
- Renal MRI or renal ultrasound
- Head magnetic resonance imaging
- Additional information for recommended screening, and surveillance and management can be found at: <http://www.tsalliance.org/pages.aspx?content=731> (Accessed February 2014)

utility of topical rapamycin for the treatment of angiofibromas. This approach holds promise, but further study is needed to establish the safety, efficacy and dosing guidelines.^{49,50}

PROTEUS SYNDROME

Proteus syndrome (MIM #176920) is a very rare condition characterized by dramatic segmental or mosaic overgrowth. Common complications include skeletal asymmetry, characteristic overgrowth of the palms or soles referred to as ‘cerebriform connective tissue nevi’ (CCTN),⁵¹ linear epidermal nevi, deep or superficial vascular malformations, dysregulated adipose tissue (formerly referred to as lipomas) and tumor predisposition (see also [Chapter 22](#)).

Cutaneous findings

Almost all individuals with Proteus syndrome have a dermatologic manifestation. Over 40% of affected neonates will demonstrate at least some evidence of the disease at birth, such as epidermal nevi or vascular malformations.⁵² The three main cutaneous findings are epidermal nevi, vascular malformations, and soft subcutaneous masses. Epidermal nevi are usually linear and verrucous, but may be macular and hyper- or hypopigmented. Malformations may be venous, capillary, and/or lymphatic.⁵³ The cerebriform connective tissue nevus, when on the sole of the foot, is caused by hyperplasia of cutaneous and subcutaneous tissues and considered virtually pathognomonic.⁵⁴ The tissue is very firm; similar lesions may also occur on the hands, perinasal area, or near the canthus. Prominent cutaneous venous structures may occur as a result of patchy dermal hypoplasia. Macrodactyly and adipose overgrowth may also be observed.

Extracutaneous findings

Overgrowth in Proteus syndrome is disproportionate, asymmetric, progressive, distorting, and persistent (see [Fig. 29.7](#)). Overgrowth usually presents between 6 and 18 months of age and can occur in areas that were completely normal at birth. Overgrowth affects most tissues including bones, cartilage, muscle, and connective tissues. At least some overgrowth and asymmetry is present at birth in 17.5% of cases.⁵² Orifices may be affected, causing respiratory obstruction, conductive hearing loss, or gastric outlet obstruction. Cystic degeneration of the lungs may lead to pneumonia.⁵⁵ Affected individuals are

BOX 29.7 DIAGNOSTIC CRITERIA FOR PROTEUS SYNDROME

General criteria: Mosaic, and progressive, and sporadic

Category A: Cerebriform connective tissue nevus

Category B:

1. Epidermal nevus
2. Disproportionate overgrowth in one: limbs, skull, external auditory canal, vertebrae, or viscera
3. Bilateral ovarian cystadenomas or monomorphic adenomas of the parotid gland in children

Category C:

1. Dysregulated adipose tissue (lipoatrophy or lipomas)
2. Vascular malformations (capillary, venous, or lymphatic)
3. Facial phenotype, all: long face, dolichocephaly, downslanting palpebral fissures, low nasal bridge, wide or anteverted nares, open mouth at rest

All three general criteria plus either one from A, two from B, or three from C are required to make a diagnosis of Proteus syndrome.

predisposed to deadly deep venous thrombosis and pulmonary embolism.⁵⁶ The central nervous system is commonly affected by hemimegalencephaly (unilateral enlargement of the brain), but most patients are asymptomatic.⁵⁷ Eye complications are common and range from strabismus to epibulbar hamartomas. Ovarian cystadenomas and cystic lesions of the epididymis are also common.

Etiology and pathogenesis

The cause of Proteus syndrome is a de novo post-zygotic activating mutation in the *AKT1* oncogene. Proteus features are an example of somatic mosaicism that is lethal in the non-mosaic state.⁵¹ Because Proteus is a mosaic disorder, biopsy of affected tissue is required to make a genetic diagnosis.

Differential diagnosis

Proteus syndrome has been overdiagnosed,⁵⁸ prompting the creation of diagnostic criteria ([Box 29.7](#)) to separate Proteus syndrome from other overgrowth syndromes, many of which share asymmetric hypertrophy as a feature but almost always to a less severe degree.⁵² Proteus stands apart by having fairly rapid postnatal progression, relentless deforming overgrowth and a poor prognosis.⁵⁸

Hemihyperplasia-multiple lipomatosis (HH-ML). This is most commonly misdiagnosed as Proteus syndrome. HH-ML includes superficial capillary vascular malformation (similar to port-wine stain), but lacks progressive, distorting overgrowth, deep vascular malformations and cerebriform connective tissue nevi on the palms or soles.⁵⁹ In non-distorting overgrowth that characterizes HH-ML, a bone is normally shaped and larger than expected, but without growths or odd edges. In HH-ML, non-distorting overgrowth is present at birth,⁵⁹ whereas, the distinctive distorting overgrowth that characterizes Proteus may not be apparent until age 2 or 3.⁵² Lipomas may recur after surgical removal. Therefore, removal of symptomatic lipomas only is recommended.

Megalencephaly-capillary malformation (MCAP). Sometimes also referred to as M-CM, it has previously been termed macrocephaly-capillary malformation and macrocephaly-cutis marmorata telangiectatica congenita. MCAP sometimes

includes markedly large brain size with variable cortical malformation, growth dysregulation with variable asymmetry, patchy capillary malformations frequently on the philtrum, upper lip and nose as well as the limbs and trunk, and distal limb abnormalities such as syndactyly and polydactyly, and mild connective tissue dysplasia (hyperextensible joints and skin).^{29,60} Congenital Chiari I malformation had been associated with MCAP, however, the term ‘cerebellar tonsil herniation’ (CTH) is now preferred to describe acquired herniation caused by cerebellar overgrowth that occurs in up to 70% of MCAP cases.⁶¹ With capillary vascular malformation and asymmetric overgrowth, children often meet the criteria for Klippel–Trenaunay syndrome. Affected children typically have developmental delay (85%) and neonatal hypotonia (68%). Frontal bossing and prominent nevus simplex are additional facial features.⁶⁰ There is also a mildly increased risk of cancer (about 3%).²⁹ MCAP has been associated with postzygotic mutations in the *PIK3CA* gene.²⁹

Mosaic overgrowth with fibroadipose hyperplasia (MOFH).

This is an example of an overgrowth syndrome defined by its newly identified causative mutation, an activating mutation in the *PIK3CA* gene.⁶² Affected children have segmental overgrowth that affects the muscles, skeleton, and fibroadipose tissue without cutaneous features of Proteus syndrome. Both distorting and non-distorting overgrowth are reported. The features of MOFH often begin at birth, in contrast to Proteus syndrome which generally appears later.⁶²

SOLAMEN syndrome. Segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus (SOLAMEN) is a ‘Proteus-like’ syndrome,⁶³ now known to be a mosaic form of Cowden disease. Affected individuals carry a germline *PTEN* mutation and a mosaic second hit to the *PTEN* gene on the opposite allele in affected tissues.⁶³ Absence of the cerebriform connective tissue nevi on the palms and soles distinguishes SOLAMEN syndrome. In addition, characteristic features of Cowden disease such as macrocephaly, breast and thyroid hamartomas and skin changes are likely to be present.⁶³

CLOVES syndrome (MIM #612918). Congenital lipomatosis, overgrowth, vascular malformations, epidermal nevi and skeletal anomalies (CLOVES) describes another subset of patients, most of whom were initially misdiagnosed with Proteus syndrome.⁵⁸ In CLOVES syndrome, overgrowth is present at birth with truncal vascular anomalies, truncal lipomatous masses and overgrown feet with acral or musculoskeletal anomalies. In contrast to Proteus, the overgrowth is not progressive.⁶⁴ Patients may have wrinkled skin on the palms and soles, but lack the firm rubbery CCTN of Proteus syndrome. Since CLOVES syndrome was suspected to be a mosaic disorder at the outset, massive DNA sequencing of affected tissues revealed causative activating mutations in *PIK3CA*.⁶⁵ Severe scoliosis, large truncal masses, high flow vascular lesions, phlebectasia with thromboembolism and orthopedic problems of the hands and feet may all require early, aggressive intervention in affected individuals.⁶⁴ Prognosis seems better compared to Proteus syndrome but this condition can still be very severe, even life-threatening.⁶⁶

Encephalocraniocutaneous lipomatosis (ECCL). The so-called ‘nevus psiloliparus’ is the cutaneous hallmark, with a

localized non-scarring patch of alopecia on the scalp which may or may not overlie a fatty tissue mass. ECCL, while once thought to be a localized form of Proteus syndrome, does not meet the diagnostic criteria of Proteus, lacking disproportionate growth³¹ as a salient feature (see also Chapter 31).

Differential diagnosis of Proteus and similar disorders

Maffucci syndrome consists of multiple enchondromatosis (which may be confused with hyperostosis) and vascular malformations.⁶⁷ Klippel–Trenaunay (MIM #149000) syndrome consists of vascular malformations with overgrowth, typically in the same segment. Axillary freckling and neurofibromas help distinguish neurofibromatosis.

Management

Management of these syndromes depends on the specific disease; if overgrowth is severe – as in Proteus syndrome – management is often very difficult. A multidisciplinary approach best addresses all aspects of the disease adequately. Ongoing ophthalmology, neurology, and developmental assessment exams are recommended.⁵² Caregivers should be informed of the risk of pulmonary embolism and stroke so that healthcare providers consider it if an emergency arises.⁵² Orthopedic surgery should be consulted before functional deficits appear and before the patient becomes too debilitated to undergo surgery. Cancer surveillance is an important part of management as dictated by clinical symptoms; routine imaging is not recommended.⁶⁸

Isolated hemihyperplasia places individuals at increased risk (5.9%) for embryonal malignancies such as Wilms tumor, adrenal cell carcinoma and hepatoblastoma.²⁸ A study of 260 children with hemihyperplasia⁶⁹ reported that the risk in truly isolated idiopathic hemihyperplasia is lower (1.2%) and in syndrome-related hemihyperplasia higher (10%) than previously reported. The risk of malignancy in specific syndromes with hemihyperplasia, including HH-ML and excluding Klippel–Trenaunay, is not clear. Until further information becomes available, screening with abdominal ultrasound every 3–6 months until age 8, checking of blood alpha fetoprotein level every 3 months until age 4 and referral to a geneticist for identifying associated syndromes is recommended.²⁸ Individuals with SOLAMEN syndrome have a risk of malignancies associated with Cowden (PTEN hamartoma) syndrome.

Additional overgrowth syndromes

Of the generalized overgrowth syndromes, Beckwith–Wiedemann Syndrome (BWS) (MIM #130650) is the most common.⁷⁰ Cutaneous features include prominent nevus simplex, distinctive anterior ear creases, and posterior helical pits. Other characteristic features are abdominal wall defects (omphalocele), placental overgrowth, macrosomia, macroglossia, kidney abnormalities, cardiomegaly, and hypoglycemia. As the phenotype is variable, mild cases are likely to be missed.⁷⁰ Mosaicism may lead to asymmetric hypertrophy of a limb or body part. BWS patients have an increased risk of Wilms tumor and hepatoblastoma.

Beckwith–Wiedemann is a disorder of imprinting, an epigenetic process using methylation to silence either the maternal or paternal allele in a gene pair. Imprinting affects only specific regions of the genome, especially areas with genes

impacting fetal growth.⁷¹ Beckwith–Wiedemann syndrome affects chromosomal region 11p15.5. This region contains an imprinting center that regulates several adjacent genes. Since 15% of cases are inherited, siblings are considered at risk for the disorder and require screening for complications. Monitoring for neonatal hypoglycemia, for example, may prevent neurologic injury. Affected children may benefit from tongue reduction surgery and speech therapy. Surveillance for abdominal embryonal tumor (described above) with ultrasound and blood testing and ongoing screening for renal abnormalities is recommended.

SIMPSON–GOLABI–BEHMEI SYNDROME TYPE I

Simpson–Golabi–Behmei syndrome type I is an overgrowth syndrome with cutaneous features including supernumerary nipples⁷² and dysplastic fingernails. The index fingers are affected with hypoplasia and nail abnormality and this characteristic feature may help in early diagnosis (Fig. 29.9).⁷² Extracutaneous features are macrosomia, macrocephaly, macroglossia, coarse square-shaped face, abdominal hernias, broad hands, and normal intelligence. The X-linked recessive disorder is⁷³ caused by a mutation in glypican-3 (*GPC3*) gene. Risk of embryonal tumors is increased and requires monitoring.

SOTOS SYNDROME

This is an overgrowth syndrome with cutaneous features including frontotemporal sparse hairs and malar flushing.⁷⁴ Other identifying features are learning disabilities, distinct facial appearance, and macrocephaly along with tall stature. The inheritance pattern is autosomal dominant caused by a



Figure 29.9 Simpson–Golabi–Behmei syndrome type I. Shortened and widened hand, post-axial polydactyly and a hypoplastic index finger (partially hidden) with absent nail in an affected 6-month-old infant.

mutation in the nuclear receptor set domain containing protein 1 gene (*NSD1*).⁷⁴

Ectodermal dysplasias

There are over 150 rare syndromes whose primary features involve alterations in two or more of the structures that derive from the embryonic ectoderm, which include developmental defects in hair, teeth, nails, sweat glands, and the lens of the eye. These are referred to as ‘ectodermal dysplasias’ (ED). The National Foundation for Ectodermal Dysplasia is an excellent resource for families and provides information to professionals caring for children with a wide variety of ED types (www.nfed.org).

HYPOHIDROTIC ECTODERMAL DYSPLASIA

Hypohidrotic ectodermal dysplasia (HED, Christ–Siemens–Touraine syndrome (MIM #305100))⁷⁵ is most often an X-linked recessive condition and is the most common form of ED encountered by clinicians.

Cutaneous findings

Patients with hypohidrotic ectodermal dysplasia often present at birth with a collodion membrane or marked scaling of the skin, which may be misconstrued as a marker of congenital ichthyosis or of postmaturity.⁷⁶ After membrane shedding, the skin is soft, thin, and light-colored with fine periorbital wrinkling (Fig. 29.10A,B). Even in the neonatal period, the hair tends to be absent or sparse, short, and blond. The nails are usually normal. Patients have an increased frequency of atopic dermatitis, particularly periorbital dermatitis.

In cases without a positive family history, repeated bouts of unexplained fevers most often bring infants with HED to medical attention. As the infants produce little to no sweat, they cannot make the appropriate physiologic response to increased environmental temperature, resulting in core temperature elevation. Diminished or absent sweat pores may be appreciated both clinically and histologically.

Extracutaneous findings

Most infants with HED have a typical facies, easily recognizable to educated family members and/or physicians, characterized by a square forehead with frontal bossing, a flattened nasal bridge with prominent nostrils, wide cheekbones with flat malar ridges, a relatively thick, everted lower lip, prominent chin, and small, pointed, low-lying ears. Lacrimal and mucous glands are hypoplastic, leading to reduced tearing, chronic thick nasal discharge, and impacted cerumen with an increased frequency of otitis media and respiratory tract infections. As the teeth are not present in the neonatal period, the typical peg-shaped or missing teeth cannot be used to aid in diagnosis, but dental X-rays can demonstrate these findings, even in young infants.

Etiology and pathogenesis

Most patients are male and carry the X-linked form; however, mutations in several individual genes with autosomal dominant and recessive inheritance patterns may lead to identical developmental abnormalities of the hair and glands. All of the involved genes are within the ectodysplasin signaling pathway (Fig. 29.11) and include ectodysplasin-A1 (*EDA-A1*), *Eda-A1*

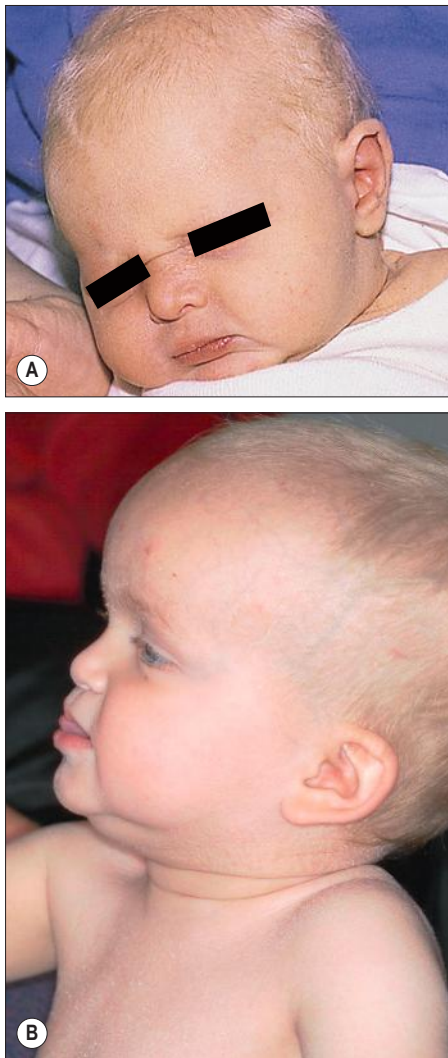


Figure 29.10 (A) A 2-week-old infant with HED syndrome. (B) 11-month-old infant with facial features characterized by a square forehead with frontal bossing, flattened nasal bridge, low-lying ears and a relatively thick, everted lower lip. Skin is thin and dry. Hair is sparse, short and blonder than siblings. (A: Reproduced with permission from Sybert VP. *Genetic skin disorders*. New York: Oxford University Press; 1997.)

receptor (*EDAR*), and *EDAR* associated death domain (*EDARADD*).^{77,78} Female carriers of ectodysplasin mutations show varied manifestations including more subtle clinical findings overall, or distinct manifestations such as hypohidrosis following the lines of Blaschko.

Differential diagnosis

Hypohidrosis may be found in another group of ectodermal dysplasias resulting from autosomal dominant mutations in p63 (Rapp–Hodgkin syndrome, AEC syndrome, EEC syndrome, limb–mammary syndrome, or ADULT syndrome), but that group has associated facial clefting and split-hand/foot malformations.^{79,80}

Treatment and care

Temperature must be carefully regulated with cool baths, air conditioning, light clothing, spray-mist bottles to dampen clothing during activities, and avoidance of warm environments (Box 29.8).⁸¹ Some families find commercially available cooling

BOX 29.8 CARE PLAN: HYPOHIDROTIC ECTODERMAL DYSPLASIA

- Avoid overheating
- Consult dentistry
- Treat ophthalmic, ENT, pulmonary, and dermatologic disease as symptoms dictate
- Recommend families contact National Foundation for Ectodermal Dysplasias (www.nfed.org)

suits to be helpful. Reduced glandular secretion may be treated with lubricating eye drops and nasal irrigation. Treatment of recurrent otitis media, respiratory infections, atopic dermatitis, and asthma should be individualized. Dental manifestations should be managed early.

HYPOHIDROTIC ECTODERMAL DYSPLASIA WITH IMMUNODEFICIENCY

Cutaneous findings

Patients with hypohidrotic ectodermal dysplasia with immunodeficiency (HED-ID) have similar findings to patients with HED although they may be less clinically obvious. They have hypohidrosis along with conical and peg-shaped teeth. They also have pale and dry or mildly scaly skin with periorbital darkening, although typically less noticeable than in patients with HED. They may also have extensive seborrheic dermatitis and intertrigo.

Extracutaneous findings

The extracutaneous findings are what help separate this disorder from HED. Patients are prone to severe and sometimes fatal infections. This can include infection with either Gram-positive or Gram-negative bacteria leading to skin and soft tissue abscesses, acute otitis media, pneumonia, osteomyelitis, gastrointestinal infections and sepsis.

Etiology and pathogenesis/management

HED-ID (MIM #300291) is most often inherited in an X-linked manner and is due to mutations in *IKBK* (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma).⁸² Autosomal dominant forms also exist and are due to mutations in *IKBα*. Both mutations result in impaired NF-κB signaling (Fig. 29.11).⁸³ Somatic mosaic mutations in *NEMO* can also occur which leads to a milder phenotype.^{83,84}

Defective NF-κB signaling is responsible for both defective ectodermal appendage development as well as the immunodeficiency in these patients. Antibody response is poor, natural killer cells are ineffective and T cells lack development and maturation which accounts for the wide variety of infectious diseases patients with HED-ID encounter.

The ED components are managed similar to those in HED; manifestations of the immunodeficiency require a multidisciplinary approach with immunologists and infectious disease specialists.

INCONTINENTIA PIGMENTI

Cutaneous findings

Incontinentia pigmenti (IP, MIM #308300)⁸⁵ is an X-linked multisystem disorder with characteristic cutaneous manifestations.

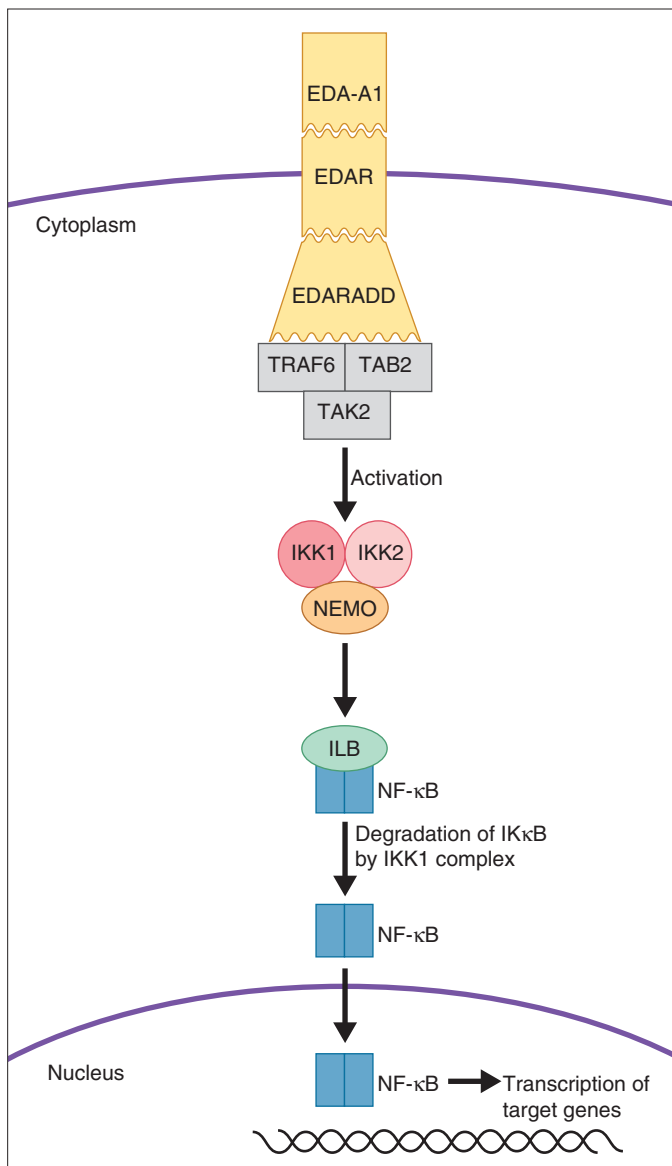


Figure 29.11 Mutations in the EDAR pathway leading to hypohidrotic ectodermal dysplasia (HED). When ectodysplasmin-A1 (EDA-A1) binds to its receptor (EDA-A1 receptor or EDAR), it leads to the formation of a complex between the EDAR associated death domain (EDARADD) and various other proteins. This complex either directly or indirectly activates IKK1/IKK2/NEMO which then degrades IκB and leaves NF-κB free to enter the nucleus and activate the transcription of various target genes. Mutations in several of these genes are associated with forms of HED as indicated.

Classically, the skin changes occur in four stages: vesicular, verrucous, hyperpigmented, and atrophic. A patient may not develop all stages and several stages may overlap.

In the newborn period, affected infants develop small, clustered blisters on an erythematous base, scattered along the lines of Blaschko (Fig. 29.12A). This stage usually resolves by 4–6 months of age, but milder, short-lived eruptions may continue during the first year of life or longer, sometimes associated with an acute febrile illness. The second phase occurs as warty, hyperkeratotic, linear lesions (Fig. 29.12B,C), typically resolving by 6 months.⁸⁵ The presence and extent of the third, hyperpigmented, stage is highly variable (Fig. 29.12D) and is often unrelated to

the distribution of the previous stages. By the age of 16 months, most pigmented lesions will have faded.⁸⁶ The last hypopigmented/atrophic stage becomes apparent with resolution of the lesions from the first three stages and demonstrates loss of hair and sweat glands. Alopecia and nail dystrophy are common.

The histopathology of IP is stage specific. Blisters show intercellular edema and intraepidermal vesicles filled with eosinophils, along with dyskeratotic keratinocytes. Patients may have peripheral eosinophilia or leukocytosis as well. Warty lesions show hyperkeratosis, papillomatosis, and mild dyskeratosis. In areas of hyperpigmentation, pigment-laden melanophages are evident in the dermis and focal dyskeratosis.

Extracutaneous findings

The most characteristic ocular finding is retinal vascular proliferation,⁸⁷ which can result in bleeding, fibrosis, retinal detachment,⁸⁸ and in 10% of patients, enough scarring to produce permanent blindness.⁸⁶ All neonates with IP need prompt and periodic evaluation by an experienced ophthalmologist. The magnitude of risk of central nervous system abnormalities is controversial but probably lower than previously believed, with current estimates varying from 10% to 30%.^{85,89} Most neurologic features present in the neonatal period and include seizures, encephalopathy, encephalitis and ischemic stroke.⁹⁰

Etiology and pathogenesis

IP results from mutations in the X chromosomal gene *IKBK* (previously known as *NEMO*, NF-κB essential modulator),⁹¹ which is involved in immune, inflammatory, and apoptotic pathways, as discussed above.⁹¹ The mutation is believed to be lethal in affected 46,XY males, but male cases have been reported in the setting of XXY genotype, and other cases in males are presumably due to somatic mosaicism or half-chromatid mutations.

Differential diagnosis

In the newborn, IP must be differentiated from other causes of blistering, including infections (bacteria and herpes simplex virus), erythema toxicum, and epidermolysis bullosa (see Chapters 10 and 11). The warty phase of IP is unique, but may be confused with a linear epidermal nevus. Linear and whorled nevoid hypermelanosis may appear identical to stage 3 of IP. Although history helps to distinguish between the two conditions, a biopsy may be necessary, as stage 3 IP has occurred as late as 15 months of age without any antecedent skin changes.

Treatment and care

The skin changes of IP do not require any treatment other than wound care for blisters to prevent secondary infection. A baseline eye examination and close follow up by an ophthalmologist and a full neurological assessment with anticipatory evaluation for the possibility of neurologic deficits are appropriate. Dental evaluation should be considered after teeth erupt.

HIDROTIC ECTODERMAL DYSPLASIA

Also known as Clouston syndrome, hidrotic ectodermal dysplasia (MIM #129500) is an autosomal dominant form of hidrotic or 'sweating' ectodermal dysplasia characterized by nail dystrophy, hyperkeratosis of the palms and soles, and hair defects.^{92,93} Affected newborns may have milky-white-appearing nails and



Figure 29.12 Incontinentia pigmenti. (A) Erythematous, linear vesicles. (B) Vesicles, verrucous plaques, and early hyperpigmentation in a neonate. (C) Verrucous phase. (D) Widespread hyperpigmentation (phase 3) in a young infant; note that a few vesicles are also present.

dry skin, or may display no clinical signs. Chronic paronychia infections frequently develop. Hair may be normal during infancy and childhood, and the diagnosis may not be recognized until abnormal sparse, fine, and brittle hair is detected or progressive nail dystrophy develops. The terminal phalanges may be tufted. Individuals show normal sweating, facies, and dentition.

Autosomal dominant mutations in connexin 30 (*GJB6*) cause the disorder.⁹⁴

The diagnosis of hidrotic ectodermal dysplasia is unlikely to be made in the newborn period in the absence of a positive family history. Nail dystrophy may be the only manifestation in one-third of patients. Swollen, tufted terminal phalanges may aid in diagnosis. One should differentiate hidrotic ectodermal dysplasia from pachyonychia congenita and other palmoplantar keratodermas (see [Chapters 19 and 32](#)).

Keratolytics and surgical debridement may be effective for keratoderma. Paronychia infections can be treated with antibiotics or anti-candidal agents as appropriate.

ECTODERMAL DYSPLASIAS DUE TO p63 MUTATIONS

Several forms of ectodermal dysplasia with overlapping clinical features are due to mutations in p63, a transcription factor that is structurally related to p53, localized to gene locus 3q27 ([Fig. 29.13](#)). These include: Rapp–Hodgkin syndrome; ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome; ankyloblepharon–ectodermal defects–cleft lip/palate syndrome; acrodermato–ungual–lacrimar–tooth syndrome; limb–mammary syndrome; and nonsyndromic split-hand/foot malformation.^{95,96} p63 is involved in epidermal development, differentiation and homeostasis. By encoding two N-termini and multiple C-termini, many different isoforms can be produced, each of which has differing functions within keratinocytes.^{97,98} For example, the $\Delta Np63$ isoform controls expression of basal layer keratins and then, upon receiving a differentiation stimulus, can change its transcriptional activity and activate genes required for cell cycle exit (IKK α).⁹⁹

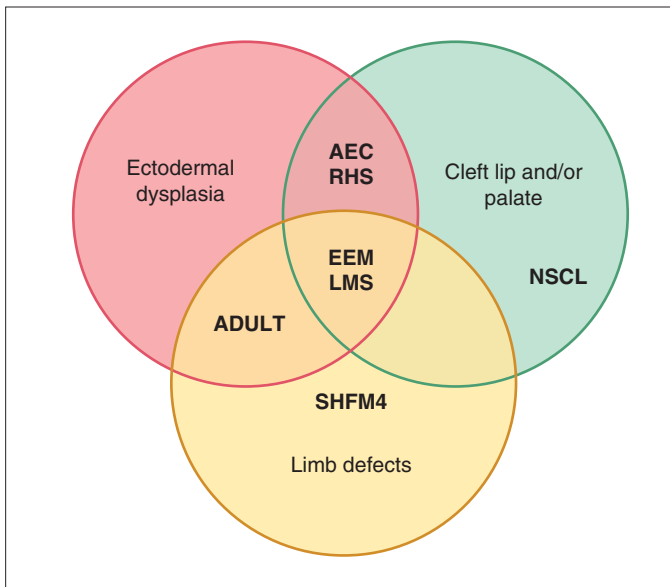


Figure 29.13 Overlapping clinical features of disorders due to mutations in *p63*. Ankyloblepharon–ectodermal defects–cleft lip/palate syndrome (AEC); Rapp–Hodgkin syndrome (RHS); ectrodactyly–ectodermal dysplasia–cleft lip/palate syndrome (EEC); limb–mammary syndrome (LMS); acrodermato–ungual–lacrima–tooth syndrome (ADULT); nonsyndromic split-hand/foot malformation (SHFM); nonsyndromic cleft lip/palate (NSCL). (Reproduced with permission from Rinne T, Brunner HG, van Bokhoven H. *p63*-associated disorders. *Cell Cycle* 2007; 6(3):262–8.)

ANKYLOBLEPHARON–ECTODERMAL DYSPLASIA–CLEFTING (AEC) SYNDROME

This syndrome (AEC, Hay–Wells syndrome, MIM #106260) is an uncommon form of ectodermal dysplasia with autosomal dominant inheritance.¹⁰⁰

Cutaneous findings

The upper and lower eyelids of the newborn have fine strands of skin between them (so-called ankyloblepharon), which are pieces of tissue that can be thick or thin, may tear spontaneously, or require surgical lysis (Fig. 29.14A). These are a cardinal feature of this condition, but are not mandatory for diagnosis. During the newborn period, the rest of the skin is erythematous and fissured with a collodion membrane appearance, resembling bullous congenital ichthyosiform erythroderma with peeling, erythema, and erosions (Fig. 29.14B) (see also Chapters 10 and 19). After the membrane has shed over the first few weeks, the underlying skin is dry and thin. Recurrent scalp infections, erosions, and granulation tissue may have their onset in early infancy and are present in two-thirds to three-quarters of older infants, children, and adults with this condition.¹⁰¹ The hair is sparse and coarse. Sweating is usually not significantly affected. Nail dystrophy is variable. The nails can be thickened and malformed, thin or absent.

Extracutaneous findings

Cleft palate, with or without cleft lip, is the third major sign of AEC syndrome, occurring in 80% of affected newborns. The reported hypodontia associated with the condition may reflect the degree of severity of the clefting, rather than a primary ectodermal defect.

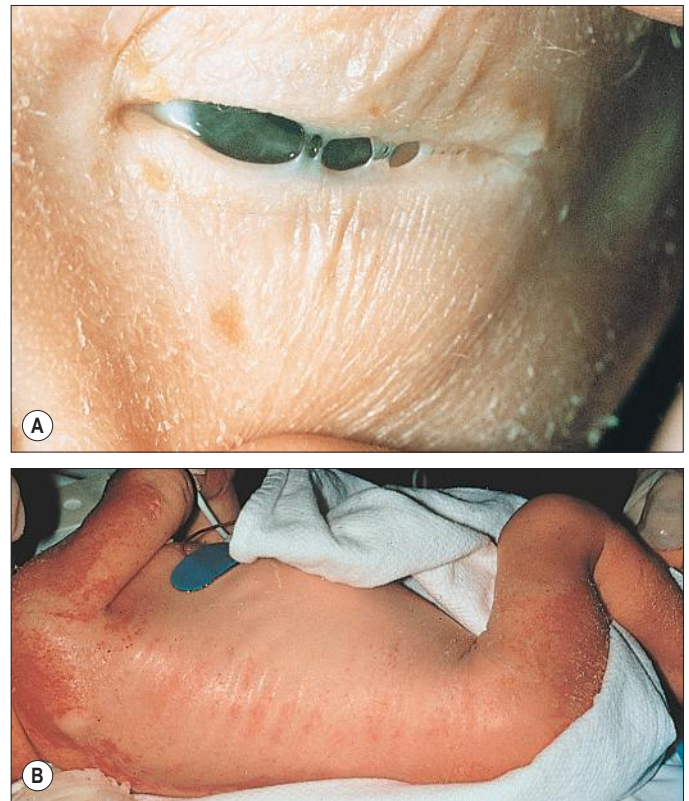


Figure 29.14 (A) Fine strands of tissue between eyelids in AEC syndrome. (B) Cracking erosions of skin on body in AEC. (A: Reproduced with permission from Sybert VP. *Genetic skin disorders*. New York: Oxford University Press; 1997. B: Adapted from Vanderhooft SL, Stephan MJ, Sybert VP. Severe skin erosions and scalp infections in AEC syndrome. *Pediatr Dermatol* 1993; 10:334–340.)

A few males with AEC have had hypospadias. External ear malformations are described in some patients. Supernumerary nipples and ectopic breast tissue occur in a minority of cases. There may be tear duct abnormalities and recurrent lid inflammation.

Differential diagnosis

Other diagnoses to be considered when presented with an infant with cleft palate and a collodion membrane include EEC (ectodermal dysplasia, ectrodactyly, cleft lip/palate syndrome), distinguished by its limb involvement, and Rapp–Hodgkin syndrome. Not surprisingly, there is considerable overlap between Rapp–Hodgkin and AEC syndromes, as they are allelic. The presence of ankyloblepharon can distinguish between the two, being a key characteristic of AEC, but now that the genetics of the conditions are appreciated, a true distinction may not be absolutely necessary.

Treatment and care

Treatment is limited to surgical management of eyelid involvement and oral facial clefting. The use of light emollients may speed the shedding of dry, cracking neonatal skin. Careful handling of the scalp and prompt attention to secondary bacterial infection may decrease long-term complications. Patients will require ongoing ocular hygiene.

ECTRODACTYLY–ECTODERMAL DYSPLASIA–CLEFTING SYNDROME (EEC)

Cutaneous findings

Cutaneous findings in EEC syndrome are mild. Fair skin and fine, sparse, light-colored hair are common features. Nails overlying abnormal, and occasionally normal, phalanges are dystrophic. Skin may be dry with occasional hypohidrosis.

Extracutaneous findings

Ectrodactyly (abnormal development of the median rays of the hands and feet) serves to distinguish this disorder from other ectodermal dysplasias and occurs in 80–100% of affected individuals. Depending on the series, cleft palate with or without cleft lip occurs in 70–100% of patients.^{102,103} Lacrimal duct hypoplasia or atresia is seen in over 90% of affected individuals, leading to excessive tearing, conjunctivitis, and blepharitis.^{104–106} Genitourinary malformations affect over one-third of patients. Chronic otitis media with secondary hearing loss occurs in 50%.¹⁰⁷

Etiology and pathogenesis

Three forms of EEC have been described, EEC1 (MIM #129900), EEC2 (MIM #602077), and EEC3 (MIM #604292). Most individuals harbor mutations in p63, a tumor-suppressor gene (see above).¹⁰⁸

Differential diagnosis

The diagnosis of EEC is self-evident when all three features (ectrodactyly, ectodermal dysplasia and clefting) are present. In the absence of limb defects, other ectodermal dysplasias associated with oral facial clefting, including Hay–Wells, Rapp–Hodgkin, and limb–mammary syndromes, need to be considered. Other diseases with limb defects include odontotrichomelic syndrome, which presents with severe absence deformities of the limbs, and Adams–Oliver syndrome (aplasia cutis congenita with limb defects), which has neither clefting nor ectodermal defects other than localized absence of skin.

Treatment and care

Treatment is mainly surgical. Consultations may include plastic surgery for cleft palate, orthopedics for limb repair, ENT for otitis media and hearing loss, ophthalmology for symptoms related to lacrimal duct hypoplasia, and urology for possible genitourinary malformations.

Disorders with skin laxity and redundant skin

Soft, hyperelastic skin, lax skin, or redundant skin, with or without bruising, fragility, or abnormal healing, is seen in a variety of related and distinct inherited disorders. Most are clinically evident in infancy or early childhood, but a correct diagnosis may be delayed until later in childhood.

CUTIS LAXA

Cutaneous findings

Cutis laxa is a term that encompasses the clinical finding of loose, inelastic skin that droops rather than stretches (Fig. 29.15), and does not spring back to place on release of tension.



Figure 29.15 Infant with cutis laxa. Droopy appearing face. (Courtesy of Dr V.P. Sybert.)

Three forms with different inheritance patterns have been described (Table 29.4). Loss of skin elasticity is progressive, and sagging may not be evident in the newborn, although in autosomal recessive disease flaccid skin is often evident at birth.¹⁰⁹ Autosomal dominant cutis laxa patients tend to develop skin laxity in later childhood.¹¹⁰

Extracutaneous findings

Cutis laxa may present in the newborn with skin changes, joint laxity, and abdominal and inguinal hernias. Pulmonary emphysema may develop either during childhood or later in the course of the disease.¹⁰⁹ In X-linked cutis laxa, bladder and gastrointestinal diverticuli can occur. Many newborns present with congenital dislocation of the hip. The characteristic long-bone and occipital exostoses (occipital horns) occur over time. Autosomal recessive disease is often more severe than the other forms, with flaccid skin evident at birth, early-onset emphysema, and vascular abnormalities such as aortic aneurysms or pulmonary artery/valve stenosis.¹⁰⁹ Death from complications related to emphysema may occur early in infancy. The autosomal dominant form typically has fewer internal manifestations and a normal associated lifespan.¹¹⁰

Etiology and pathogenesis

The inherited forms of cutis laxa are detailed in Table 29.4.

Differential diagnosis

Ehlers–Danlos syndrome (EDS) has similar skin laxity, but has the elastic recoil lacking in cutis laxa. Unlike in EDS, vascular fragility and problems with wound healing are lacking. Cutis laxa may also present as a component of other genetic disorders. Acquired cutis laxa is often late onset and associated with drug exposure to penicillin, d-penicillamine, or isoniazid. Alternatively, acquired disease may develop from crops of well-demarcated inflammatory plaques in association with fever, malaise, and peripheral neutrophilia or eosinophilia.¹¹¹ This form, which has sometimes been called ‘Marshall syndrome’ has been reported in infancy.¹¹² Areas of loose wrinkled skin are also evident in the so-called ‘prune belly syndrome’ where lax skin is seen in association with renal anomalies and hypoplastic abdominal musculature (Fig. 29.16).¹¹³

The diagnosis is confirmed by elastin staining (Verhoeff–van Gieson, orcein) of a skin biopsy. X-linked disease has

TABLE
29.4

Disorders to consider in the differential diagnosis of cutis laxa

Disease name	Gene symbol	MIM #	Inheritance	Clinical findings			
				Cutis laxa	Emphysema	Aneurysms	Developmental delay
ALDH18A1-related cutis laxa	ALDH18A1	612652	AR	+	–	–	++
FBLN5-related cutis laxa	FBLN5	219100	AR	+++	+++	–	–
EFEMP2-related cutis laxa	EFEMP2 (FBLN4)	219100	AR	++	++	+++	–
Autosomal recessive cutis laxa type 2A	ATP6V0A2	278250	AR	++	–	–	++
Autosomal dominant cutis laxa	ELN or FBLN5	123700	AD	+	+	+	–
Geroderma osteodysplastica	GORAB	231070	AR	++	–	–	–
De Bary syndrome (PYCR1-related progeroid syndrome)	PYCR1	219150	AR	+	–	–	+++
Autosomal recessive cutis laxa type 2B	PYCR1	612940	AR	+	–	–	+++
LTBP4-related cutis laxa	LTBP4	613177	AR	+	++	+	+
RIN2-related cutis laxa	RIN2	613075	AR	+	–	–	±

(Reproduced with permission from Van Maldergem L, Dobyns W, Kornak U. ATP6V0A2-Related Cutis Laxa. 2009 Mar 19 [Updated 2011 May 10]. In: Pagon RA, Bird TD, Dolan CR, et al. editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK5200/>)



Figure 29.16 'Prune-belly' syndrome. Note the distended abdomen with prominent skin laxity.

abnormally large collagen fibrils with normal elastic fibers, whereas autosomal disease has reduced elastin, an abnormal dense amorphous component, and variation in collagen fibril diameter with collagen 'flowers.' Low serum ceruloplasmin or copper levels may also help in the diagnosis of affected boys.¹⁰⁹

Treatment and care

All patients should have a complete physical examination for associated abnormalities, chest radiography to screen for emphysema and cardiomyopathy, and echocardiography for potential cardiac valve involvement (Box 29.9). Pulmonary function tests should be considered for early detection of emphysema. As solar elastosis aggravates cutaneous disease, sun protection should be emphasized.¹¹⁴ Early parenteral copper-histidine replacement may prolong life and delay the onset of symptoms in patients with the X-linked form.¹¹⁵

DE BARSY SYNDROME

This rare condition is characterized by very lax, wrinkled skin and a progeroid facies with thin hair, thin skin, and lack of subcutaneous fat, all present at birth without progression over time. A prominent vascular pattern is probably due to the thin dermis. Affected infants also have intrauterine growth

BOX 29.9 CARE PLAN: CUTIS LAXA

- Complete physical examination
- Chest X-ray
- Consider pulmonary function tests
- Echocardiogram
- Surgical consult for diverticuli, rectal prolapse, and hernias
- Sunscreen protection
- Possible parenteral copper-histidine replacement (X-linked)

retardation and poor postnatal growth. The hands are held in fists, whereas other joints are typically lax. Mental retardation is present; choreoathetosis develops over time. Eye findings include cataracts, strabismus, and myopia. De Bary syndrome has an autosomal recessive inheritance pattern and is associated with mutations in the *P5CS* and *PYCR1* genes.¹¹⁶

EHLERS–DANLOS SYNDROMES

The Ehlers–Danlos syndromes (EDS) are a group of inherited connective tissue disorders characterized by articular hypermobility, skin extensibility, and tissue fragility. A significant number of individuals with all types of EDS have cardiac abnormalities.¹¹⁷ They were originally classified as 11 separate disorders,¹¹⁸ however, as the genetic mutations underlying this group of disorders are becoming elucidated, the classification has been updated (Table 29.5).^{119–121}

Cutaneous findings

Babies with the classic type of EDS have soft, velvety, extensible skin that feels doughy and is very fragile with bruising and splitting secondary to minimal trauma. Wounds are slow to heal, quickly dehisce, and often resolve with cigarette paper-like atrophic scars. Patients with kyphoscoliosis-type and arthrochalasia-type EDS have less prominent skin fragility, bruisability, and dermal hyperextensibility than those with classic EDS.¹¹⁷ Patients with the periodontal form have similar skin findings to those in classic EDS, but additionally have excessive wrinkling of the palms and soles. Over time, the skin becomes hyperpigmented and markedly atrophic. In dermatosparaxis-type EDS a patient's skin is characterized by extreme fragility and is sagging, redundant, and not in-elastic.

TABLE
29.5

Clinical features, inheritance patterns, and biochemical defects of the Ehlers–Danlos syndromes

Villefranche classification (1997) ¹¹⁹	Disease	Cutaneous features	Extracutaneous features	Inheritance	Gene
Classic type	EDS type I/II	Soft, hyperextensible skin; thin atrophic scars	Hypermobility joints, prematurity	AD	COL5A1
	EDS type I/II			AD	COL5A2
	EDS type I			AD	COL1A1
Hypermobility type	EDS type III	Soft skin	Large and small joint hypermobility	AD	TNXB
	EDS with tenascin-X deficiency			AR	TNXB
Vascular type (Sack–Barabas)	EDS type IV	Thin, translucent skin with visible veins; easy bruising; absence of skin and joint extensibility	Arterial, bowel, and uterine rupture, characteristic facial appearance, pneumothorax, positive family history of sudden death	AD	COL3A1
Kyphoscoliosis type	EDS type VIA	Soft, hyperextensible skin, tissue fragility, easy bruising	Muscle hypotonia, scoliosis, joint laxity, Marfanoid habitus, microcornea	AR	PLOD1
	EDS type VIB			AR	ZNF469
Arthrochalasia type	EDS type VIIA	Severe skin fragility; sagging redundant skin	Congenital hip dislocation, severe joint hypermobility	AD	COL1A1
Dermatosparaxis type	EDS type VIIB			AD	COL1A2
	EDS type VIIC			AR	ADAMTS2
Other variants	Cardiac valvular EDS with COL1A2 deficiency	Skin hyperextensibility, atrophic scarring	Severe cardiac valvular disease, joint hypermobility, blue sclera, increased bone fragility	AR	COL1A2
	Brittle cornea syndrome 1	Skin hyperelasticity	Blue sclera, corneal rupture after minor trauma, keratoconus, keratoglobus, joint hypermobility	AR	ZNF469
	Brittle cornea syndrome 2	Skin hyperelasticity	Blue sclera, corneal rupture after minor trauma, keratoconus, keratoglobus, joint hypermobility	AR	PRDM5
	EDS, musculocontractural type, D4ST1-deficient type EDS	Skin hyperextensibility, wrinkled palms, easy bruising, atrophic scarring	Craniofacial dysmorphism, variable ocular involvement, joint contractures of fingers, clubfeet, severe kyphoscoliosis, muscular hypotonia, joint hypermobility	AR	CHST14
	FKBP14-deficient type, EDS type VIB			AR	FKBP14
	EDS, progeroid form, EDS with XGPT			AR	B4GALT7
	EDS, spondylocheiro-dysplastic form (SCD-EDS)	Thin, hyperelastic skin, finely wrinkled palms	Postnatal growth retardation, short stature, protuberant eyes with bluish sclerae, tapering fingers, thenar muscle atrophy, joint hypermobility	AR	SLC39A13

Rather than having the extensible and doughy skin seen in classic EDS, the skin in vascular-type EDS is thin and translucent with a visible vascular pattern (Fig. 29.17). It is not fragile and heals normally, but bruising is still common. Patients have a typical facial appearance, characterized by a thin nose, thin lips, and prominent eyes. Unless the disorder is already known to be in the family, none of these features is likely to be appreciated in the newborn or young infant.

Extracutaneous findings

Of the neonates with EDS, 40% are delivered prematurely.¹²² All forms of EDS have joint hypermobility with joint dislocations; congenital dislocation of the hip occurs in the classic, vascular, and arthrochalasia types. Although the prevalence is unknown, cardiac and aortic abnormalities seem to be much more common than in the general population. This is most evident in patients with the vascular type of EDS, who are at high risk for rupture of medium-sized arteries, aorta, and bowel, either spontaneously or following minor trauma. Special precautions should be taken when performing surgery on these patients.

Etiology and pathogenesis

The pathogenesis and inheritance patterns of EDS are detailed in Table 29.5.

Differential diagnosis

Cutis laxa also has hyperextensible skin, but it is loose and sagging, whereas the skin in EDS is elastic and recoils. Although patients with Marfan syndrome may also have mild to moderate joint hypermobility, the skin in newborns with Marfan syndrome does not show distinctive findings in this age group as it may with EDS.

Treatment and care

Treatment of EDS is mostly supportive and preventative (Box 29.10). Large doses of ascorbic acid (a cofactor of lysyl hydroxylase), 2–4 g/day, have been used in patients with kyphoscoliosis-type EDS, with clinical response.¹²³ Specific therapies are not routinely used in other subtypes, although some physicians recommend high-dose ascorbic acid for all subtypes.¹²⁴



Figure 29.17 Prominent visible venous pattern in EDS IV. (Reproduced with permission from Sybert V.P. *Genetic skin disorders*. New York: Oxford University Press; 1997.)

BOX 29.10 CARE PLAN: EHLERS–DANLOS SYNDROME

- Genetic counseling
- Orthopedic consultation for joint dislocation
- Echocardiogram at diagnosis
- Skin protection from trauma

A cardiovascular examination should be performed on all patients. Those with evidence of abnormalities or any patient with the vascular form of EDS should have an echocardiogram (Box 29.10). Alternatively, some recommend echocardiography at diagnosis for all patients, to assess aortic size.¹¹⁷

Because of tissue friability, surgical procedures are difficult, with dehiscence and wound breakdown being common. Although scars will still spread over time, a combination of adhesive tape, skin closure surgical adhesive tape, absorbable running subcuticular suturing, increased density of sutures, or cyanoacrylate adhesives may facilitate healing. Pseudotumor formation may be prevented by applying pressure bandages to hematomas. Parents should be instructed on how to protect the infant from trauma.

Mosaic disorders

The understanding of the genetics of mosaicism and its impact on skin development is increasing. In general, asymmetric and/or linear skin changes may be attributed to mosaicism, which can be the result of distinct cell lines or X inactivation. Female carriers of X-linked disorders such as incontinentia pigmenti express pigment changes along the lines of Blaschko. Children mosaic for chromosomal aneuploidy may have hyperpigmentation or hypopigmentation along the lines of Blaschko, or in other patterns, such as a phylloid (leaf-like) or checkerboard appearance. These cutaneous patterns represent the endpoint of cell migration during embryogenesis.

FOCAL DERMAL HYPOPLASIA OF GOLTZ

Cutaneous findings

Focal dermal hypoplasia (FDH, MIM #305600) is characterized by congenital linear or reticulated atrophic, hypo- or

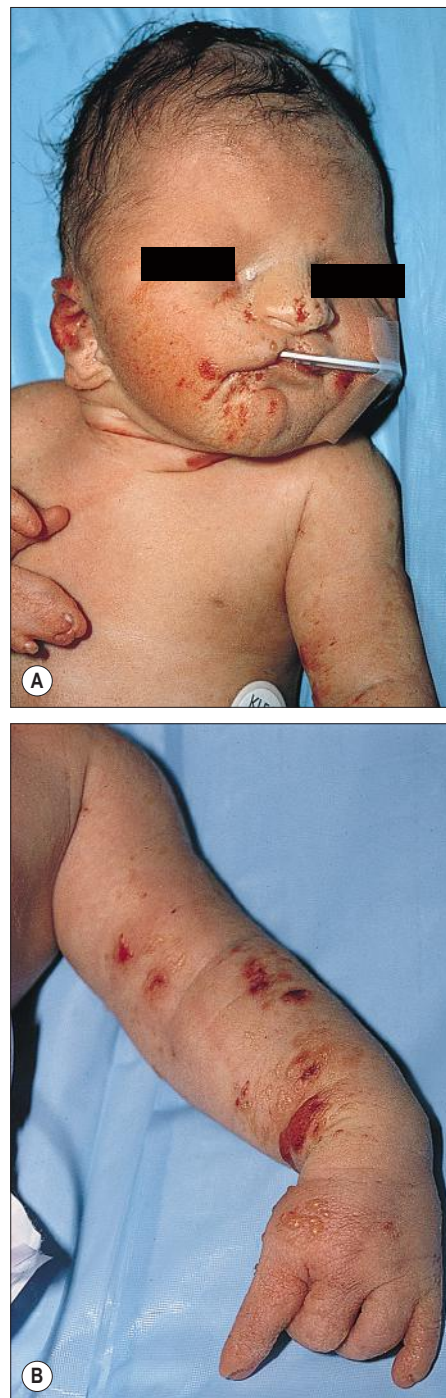


Figure 29.18 (A) Streaky areas of atrophy in focal dermal hypoplasia of Goltz syndrome. Note syndactyly. (B) Linear fat herniation with vesiculation.

hyperpigmented lesions following the lines of Blaschko, often with prominent telangiectasias (Fig. 29.18A).^{125,126} Fat herniations, hyperkeratosis, aplasia cutis, and scarring with pinpoint, pore-like depressions may occur within these lesions (Fig. 29.18B).¹²⁷ The skin lesions are usually regarded as essential for the diagnosis, but cases without skin involvement have been reported.¹²⁸ Biopsy of affected areas reveals dermal hypoplasia with upward extension of subcutaneous fat almost to normal epidermis.

Other common findings include raspberry-like papillomas, which are commonly found on the perineum, vulva, anus, or lips. These vascular papillomas usually develop over time, but may be present at birth.¹²⁹ Nails are often dystrophic, and hair may be sparse and brittle.

Extracutaneous findings

After skin disease, skeletal abnormalities constitute the second most constant manifestation of FDH and include limb reduction, asymmetric growth, small stature, and split-hand/split-foot malformations ('lobster-claw' deformity).¹²⁷ Vertical striations in the metaphyses of long bones (osteopathia striata) may be seen in many patients and are a useful index for diagnosis.^{130,131} Ocular abnormalities affect approximately 40% of patients and range from strabismus to microphthalmia.¹²⁷ Teeth are commonly malformed or absent. Less commonly described findings include clavicular anomalies, abdominal wall defects, renal anomalies, and congenital heart defects.^{127,132,133}

Etiology and pathogenesis

FDH is X-linked dominant and presumed lethal in hemizygous males. It is due to mutations in the *PORCN* gene which encodes a protein important in Wnt signaling.^{134,135} Lyonization of the X chromosome may explain the cutaneous Blaschko linear distribution. Rare cases in males may arise from somatic mosaicism and half-chromatid mutations.¹³³

Differential diagnosis

The diagnosis of FDH is clinical, with histologic and radiographic corroboration (see above). Skin lesions of FDH do not blister and are static in comparison with IP. There is no epiphyseal stippling in FDH as in Conradi–Hunermann–Happle syndrome (X-linked dominant chondrodysplasia punctata), which also has linear ichthyosis and follicular atrophoderma as opposed to the telangiectases, hypo-/hyperpigmentation, and/or dermal atrophy of FDH. Distal extremities are not involved in MIDAS (microphthalmia, dermal aplasia, and sclerocornea) syndrome, and herniations of fatty tissue are not found. The initial skin changes of linear porokeratosis and porokeratotic eccrine and ostial dermal duct nevus may also resemble FDH, but evolution over time and histopathology can help to distinguish these conditions.

Treatment and care

After a complete physical examination looking for possible systemic manifestations, the management of FDH is mainly symptomatic. Infants should be evaluated by dermatology, ophthalmology, and orthopedic surgery as needed because of the common occurrence of skeletal, cutaneous, and ophthalmologic disease. Other anomalies should be investigated in symptomatic individuals.

EPIDERMAL NEVUS SYNDROME

The sporadic association of epidermal nevi (see also [Chapter 26](#)) with developmental abnormalities in other organ systems constitutes epidermal nevus syndrome (ENS, MIM #163200).

Epidermal nevi vary according to their predominant component and include nevus sebaceus (sebaceous glands), nevus comedonicus (hair follicles) and verrucous nevus (keratinocytes). The mosaic genetic variations underlying these conditions are beginning to become clear. Somatic mosaic mutations

in RAS have been identified in keratinocytic and sebaceous epidermal nevi.^{136,137} Multiple other mucocutaneous findings may occur simultaneously with the epidermal nevus. Central nervous, ocular, and musculoskeletal systems are predominantly affected, however, a wide range of abnormalities may occur within each of these systems, and occasionally other organ systems may be involved. ENS occurs sporadically and should be considered in any patient with extensive epidermal nevi or epidermal nevi associated with systemic abnormalities. The possibility that an epidermal nevus is a component of another syndrome, such as Proteus, CHILD (congenital hemidysplasia with ichthyosiform nevus and limb defects), or phakomatosis pigmentovascularis, should be considered. Patients suspected of having ENS should have a thorough physical evaluation with special attention to the musculoskeletal, neurologic, ocular, and cardiovascular systems. Depending on the findings of the physical examination, management should be multidisciplinary.

MIDAS SYNDROME

Microphthalmia, dermal aplasia, and sclerocornea (MIM #309801) are the hallmarks of MIDAS or MLS (microphthalmia and linear skin defects). Dermal aplasia typically presents as atrophic linear scars on the face, scalp, and neck ([Fig. 29.19](#)).¹³⁸ The skin shows irregular, linear, erythematous areas of atrophic skin similar in appearance to fresh lesions of aplasia cutis congenita. Eye defects are usually bilateral and include microphthalmia, corneal opacities, and orbital cysts. Congenital heart disease and neurologic abnormalities may be found.¹³⁹

MIDAS syndrome is an X-linked dominant disorder caused in some cases by a deletion in *HCCS*, which encodes mitochondrial holocytochrome c-type synthase.¹⁴⁰ This hampers oxidative phosphorylation and regulation of apoptosis which results in the clinical phenotype.

In contrast to FDH, aplastic skin lesions are limited to the upper half of the body. Fat herniation and other manifestations of FDH, such as papillomas, clefting of the hands or feet, syndactyly, and coloboma, do not occur in MIDAS syndrome.

Patients should have complete physical and ophthalmic examinations, with treatment individualized to the patient.



Figure 29.19 Microphthalmia/linear skin defects. Atrophic linear scars on the face and neck.

BOX 29.11 CLINICAL FEATURES: TURNER SYNDROME

DERMATOLOGIC ASSOCIATIONS

- Congenital lymphedema
- Low posterior hairline
- Webbed neck
- Pigmented nevi
- Cutis verticis gyrata
- Hypoplastic, concave nails

EXTRACUTANEOUS MANIFESTATIONS

- Gonads:
 - Infertility
 - Streaked gonads
- Musculoskeletal:
 - Short stature
 - Shield chest
 - Widely spaced nipples
 - Micrognathia
- Cardiac malformations:
 - Bicuspid aortic valve
 - Coarctation
- Renal malformations
- Endocrine
- Hypoglycemia in infancy
- Growth hormone deficiency
- Autoimmune thyroiditis



Figure 29.20 Turner syndrome resulting in excessive folding of nuchal skin. (Reproduced with permission from Charrow J. A 1-year-old girl with 'puffy feet.' *Pediatr Ann* 2006; 35:546–548.)

Chromosomal disorders

TURNER SYNDROME

Turner syndrome (Ullrich–Turner syndrome) occurs in approximately 1 in 3000 females and is caused by absence or partial deletion of one of the X chromosomes. Lymphedema, neck webbing, short stature, gonadal dysfunction, and cardiac malformations are the characteristic features (Box 29.11).

Cutaneous findings

Lymphatic abnormalities are a common presenting manifestation of Turner syndrome (TS). Fetal edema, viewed on ultrasound, can lead to the prenatal diagnosis. Any infant presenting with congenital lymphedema of the extremities or neck requires a karyotype analysis. Lymphatic defects result in many clinical manifestations, including pterygium coli (webbing of the neck), redundant neck folds, and a low hairline over the nape (Fig. 29.20).¹⁴¹ Nails may become hypoplastic and concave, with an increased insertion angle secondary to lymphedema.¹⁴² Cutis verticis gyrata or congenital areas of fixed skin folds are also presumed to be caused by in utero entrapment and fixation of edematous skin.¹⁴³ Acral edema usually resolves by 2 years of age, but may persist or recur in childhood in a minority of patients. No sequelae of lymphedema, such as cellulitis or elephantiasis nostras verrucosa, have been reported.¹⁴¹

Benign melanocytic nevi are increased in number in TS, with one study showing the average number of nevi to be 115,¹⁴⁴ versus 20–40 per person in the general population.¹⁴⁵ The nevi are not dysplastic clinically or histologically, and patients do not appear to have an increased risk of developing malignant melanoma.¹⁴⁶ Other cutaneous stigmata including alopecia areata, café-au-lait macules, a tendency to form keloids, psoriasis, and vitiligo are of questionable increased frequency.¹⁴¹ A subset of patients who are mosaics for their chromosome alterations present with pigmentary alterations along the lines of Blaschko.

Extracutaneous findings

The physical phenotype of patients with TS is highly variable, with many patients appearing physically normal except for short stature.¹⁴⁷ Nevertheless, several clinical features related to bone deformities may be found, including a square-shaped 'shield' chest with widely spaced nipples, cubitus valgus, chondrodysplasia of the distal radial epiphysis (Madelung's deformity), and brachymetacarpalia/tarsalia.¹⁴¹ Additional features include micrognathia, downward displacement of the outer corner of the eyes and epicanthic folds, low-set ears, and a high arched palate.

Etiology and pathogenesis

Turner syndrome is a sporadic disease of females characterized by the absence of all or part of the second X chromosome. TS is often diagnosed incidentally by amniocentesis or chorionic villous sampling performed for unrelated reasons.¹⁴⁸ However, many infants are diagnosed prenatally based on the ultrasonic finding of fetal edema or an abnormal marker screen. Other ultrasonic findings may include nuchal translucency, cystic hygroma, coarctation of the aorta, renal anomalies, growth retardation, and fetal hydrops.¹⁴⁹ Up to one-third of affected girls are diagnosed at birth based on puffy hands and feet or redundant nuchal skin.¹⁴⁸ Another third have edema at birth, but it is commonly overlooked until adolescence or adulthood.

Differential diagnosis

The main differential is Noonan syndrome, SHOX haploinsufficiency¹⁵⁰ or other chromosomal abnormalities leading to short stature.¹⁵⁰

Treatment and care

Baseline evaluation of patients diagnosed with Turner syndrome should include physical examination, echocardiography,

BOX 29.12 CLINICAL FEATURES: TRISOMY 21**DERMATOLOGIC ASSOCIATIONS**

- Cutis marmorata
- Transient neonatal leukemoid reaction
- Elastosis perforans serpiginosa
- Multiple syringomas
- Milia-like calcinosis
- Alopecia areata
- Folliculitis
- Psoriasis

EXTRACUTANEOUS MANIFESTATIONS

- Short stature
- Hypotonia
- Cardiac malformations:
 - Ventral septal defect
 - Atrioventricular communis
- Duodenal atresia
- Mental retardation
- Alzheimer disease
- Leukemia

renal ultrasound, thyroid function tests, and a hearing screen. Patients should also be monitored for ovarian failure, growth issues, and psychosocial issues.^{148,151}

TRISOMY 21

In 1959, Down syndrome (MIM #190685) was found by Lejeune and colleagues¹⁵² to be caused by the presence of three copies of chromosome 21. In most instances, trisomy 21 is sporadic, the risk increasing with increased maternal age. The chromosome has been sequenced and is estimated to contain over 200 genes.¹⁵³ Despite considerable effort to determine which features, if any, of trisomy 21 are due to dosage effects of specific genes, none have so far been identified.

There are many phenotypic changes associated with trisomy 21 (Box 29.12). One feature relevant to evaluation in the newborn period is a pustular eruption which can occur in the setting of a transient neonatal leukemoid reaction, which occurs in as many as 10% of newborns with trisomy 21.¹⁵⁴ Most cases resolve spontaneously; however, children with trisomy 21 are also at risk for the development of acute leukemia, both ALL and AML (see Chapter 10). Other cutaneous associations in trisomy 21 include elastosis perforans serpiginosa, multiple syringomas, alopecia areata, milia-like idiopathic calcinosis cutis, and crusted scabies, and psoriasis but these rarely if ever occur in the neonatal period or early infancy.^{155,156}

TRISOMY 18

Trisomy 18 (Edwards syndrome) occurs in approximately 1 in 3600–8500 live births. It is fatal by 1 year of age in 90% of cases. Characteristic features (Box 29.13) include overriding fingers, nail hypoplasia, short hallux, and distinctive facial appearance. Neurologic features include cerebellar hypoplasia and agenesis of the corpus callosum.¹⁵⁷ Skin involvement may include redundancy and hirsutism of the forehead and back. Cutis marmorata and scalp defects have also been reported. G-banded karyotype or aneuploidy fluorescent in situ hybridization analysis can be used to confirm the diagnosis. The differential diagnosis includes fetal akinesia sequence, which is characterized by

BOX 29.13 CLINICAL FEATURES: TRISOMY 18**DERMATOLOGIC ASSOCIATIONS**

- Skin redundancy
- Cutis marmorata
- Hirsutism of forehead and back
- Nail hypoplasia
- Low arch dermal ridge pattern on fingertips
- Scalp defects (rare)

EXTRACUTANEOUS MANIFESTATIONS

- Cerebellar hypoplasia
- Agenesis of corpus callosum
- Malformed ears
- Overriding fingers/clenched hand
- Short sternum
- Cardiac defects

polyhydramnios, characteristic facial features, joint contractions, and overriding fingers.

TRISOMY 13

Trisomy 13 (Patau syndrome) was first reported in 1960 and is a cause of multiple congenital anomalies occurring in approximately 1 in 10000–20000 live births (Box 29.14). Orofacial clefts, holoprosencephaly, microphthalmia, and postaxial polydactyly are the cardinal features, with parieto-occipital aplasia cutis of the scalp also being a diagnostic feature. Minor findings include hemangioma on the forehead, anterior cowlick, loose skin, and abnormal ears.¹⁵⁷

Miscellaneous disorders**CEREBELLO-TRIGEMINAL DERMAL DYSPLASIA**

Cerebello-trigeminal dermal dysplasia (Gomez–Lopez–Hernandez syndrome, MIM #601853)¹⁵⁸ is a rare condition characterized by bilateral localized scalp alopecia and cerebellar malformation (rhombencephalosynapsis) with variable trigeminal nerve anesthesia.¹⁵⁹ Alopecia appears on the scalp at birth in a band-like pattern, most often symmetrically in the parieto-occipital region. The alopecia might be mild and easily hidden, asymmetric or unilateral.¹⁵⁹ In addition, facial scars may develop later in life, secondary to self-injury from trigeminal anesthesia. Patients may have retardation of motor and mental development. Anesthesia may occur in the trigeminal distribution and cornea leading to corneal opacities. Variably, the skull is asymmetric, with midfacial hypoplasia and low-set ears. Fifth finger clinodactyly, corneal opacities, and short stature have been associated.¹⁵⁸ Cerebellar alterations can be detected clinically with characteristic structural abnormalities seen on both CT and MRI.¹⁵⁸ Expressivity is highly variable with mild cases easily missed.¹⁶⁰ Failure of migration and multiplication from a specific ectodermal region have been hypothesized to cause this syndrome.¹⁶¹ All cases have been sporadic with more affected boys than girls.^{160,159} The differential diagnosis includes healed areas of aplasia cutis congenita; however, other signs of disease become evident in patients with cerebello-trigeminal dermal dysplasia as the individuals age. Neurology consultation for evaluation and treatment of motor development delay, neuropsychiatric evaluation and ophthalmology evaluation for corneal abnormalities is recommended.

BOX 29.14 CLINICAL FEATURES: TRISOMY 13**DERMATOLOGIC ASSOCIATIONS**

- Scalp defects (parieto-occipital)
- Loose skin on posterior neck
- Transverse palmar crease on hand
- Hyperconvex narrow fingernails
- Forehead hemangioma

EXTRACUTANEOUS MANIFESTATIONS

- Cleft lip/palate
- Holoprosencephaly
- Polydactyly
- Abnormal helices
- Deafness
- Cardiac ventricular septal defect
- Cryptorchidism

FAMILIAL DYSAUTONOMIA

Familial dysautonomia (Riley–Day syndrome, hereditary sensory and autonomic neuropathy type III; MIM #223900) is an autosomal recessive condition seen almost exclusively in Ashkenazi Jews (Box 29.15). The USA has the largest prevalence of familial dysautonomia in the world related to a founder mutation.¹⁶² Due to population-based genetic screening for at-risk couples, and use of reproductive technology such as pre-implantation genetic diagnosis, the number of newborns with familial dysautonomia has steadily dropped.^{163,164} Familial dysautonomia causes progressive systemic sensory and autonomic dysfunction. Excessive drooling and sweating, and blood pressure dysregulation are common. Survival is reduced, and almost one-fifth of those affected die in infancy or childhood.

Cutaneous findings

Absent tearing, a cardinal feature of Riley–Day syndrome, is usually not appreciated in neonates, as overflow tearing does not develop until 2–3 months of age in normal infants. Affected babies may have striking blotching and mottling of the skin. This usually appears one month after birth and within the first year, as do bouts of hyperpyrexia. Emotional excitement often precipitates the appearance of red blotches. The hands and feet may be cool and mottled from vasoconstriction, or swollen and red from vasodilation. In familial dysautonomia, indifference or insensitivity to pain results in progressive self-mutilation, burns, and ulcers. Absent fungiform papillae on the tip of the tongue are an important diagnostic feature and the associated absence of taste buds leads to decreased ability to taste, especially sweetness. Insensitivity to pain causes oro-dental-self-mutilation of the tongue, lips and cheeks or loss of teeth. Compulsive biting in those areas may cause tumor-like masses called Riga–Fede disease (see Fig. 30.14), or ulcers. In toddlers, injuries to the tongue from emerging teeth are common.

Extracutaneous findings

Although usually not diagnosed until several years of age, generalized signs appear within the newborn period in over 80% of patients.¹⁶⁵ These signs include breech birth in one-quarter, prematurity, intrauterine growth retardation, hypotonia, respiratory insufficiency, and poor feeding with swallowing difficulty and aspiration, developmental delay, short stature, scoliosis and corneal disease. Unexplained episodes called ‘dysautonomic crises’ of fever, labile blood pressure, tachycardia, aspiration

BOX 29.15 CLINICAL FEATURES: RILEY–DAY SYNDROME**DERMATOLOGIC ASSOCIATIONS**

- Macular erythema
- Hyperhydrosis
- Lack of pain sensation
- Absent fungiform papillae

EXTRACUTANEOUS MANIFESTATIONS

- Scoliosis
- Hypersalivation
- Hypotonia
- Alert expression

pneumonia, and vomiting are typical. Deep tendon reflexes are invariably absent. Dysmorphic facial features are not associated, but facial asymmetry and a straightened mouth develop due to abnormal tone and molding of the facial bones.¹⁶³

Etiology and pathogenesis

The causative gene for familial dysautonomia syndrome is the *IKBKAP* (I-kappa-B kinase complex associated protein) gene on chromosome 9q31. Disease expression is variable even though 99.5% of affected children have the same homozygous mutations.¹⁶⁶ The cause is decreased survival of certain sensory, sympathetic, and parasympathetic nerve cells.

Differential diagnosis

In an infant with unexplained hyperpyrexia, abnormal sweating, and failure to thrive, the primary differential diagnosis is hypohidrotic ectodermal dysplasia versus familial dysautonomia syndrome. Injection of histamine (1:10000) does not elicit a flare response in familial dysautonomia. The flare response can discriminate between the two conditions, as can the presence of teeth on a Panorex examination of the jaw. Further, in familial dysautonomia, the pupil is hypersensitive to parasympathomimetic drops like methacholine and pilocarpine. Upon exposure, the pupil almost always shrinks in familial dysautonomia, but not in a normal eye. The astute physician, aware of the feature of random blotching and mottling of the skin, may be able to make the diagnosis of Riley–Day syndrome in an infant whose multiplicity of problems have eluded correct diagnosis.

Treatment and care

Due to poor coordination, breast-feeding is difficult and delivery of proper nutrition might require a nasogastric tube or possible gastrostomy tube in the first year.¹⁶³ Use of artificial tears, and avoidance of aspiration are necessary. Referral to neurology and orthopedics for specialized care is recommended. The involvement of multiple subspecialists in addition to close follow-up with the primary care provider is important.

COFFIN–SIRIS SYNDROME

A heterogenous disorder, hypoplastic or absent fifth digits or nails are the most consistent feature of Coffin–Siris syndrome (MIM #135900).¹⁶⁷ Hypertrichosis, thick eyebrows and long eyelashes (see Chapter 31) with sparse temporal and frontal scalp hair characterize the most common ‘classic/Type A’, but thin ‘penciled’ eyebrows characterize the more rare ‘Type B’

BOX 29.16 CLINICAL FEATURES: COFFIN–SIRIS SYNDROME**DERMATOLOGIC ASSOCIATIONS**

- Hypertrichosis
- Low frontal hairline
- Bushy eyebrows
- Sparse scalp hair
- Absence or hypoplasia of nails on fifth finger and toe

EXTRACUTANEOUS MANIFESTATIONS

- Facies:
 - Coarse features
 - Broad nose
 - Wide mouth, thick lips
- Hypoplastic or absent fifth finger distal phalanx
- Low birthweight
- Growth failure
- Mental retardation

variant (Box 29.16).¹⁶⁷ Developmental delay and mental retardation are necessary to make the diagnosis. The facial features of Coffin–Siris fall into two groups with coarse facial features, thick eyebrows and thick lips characterizing ‘Type A’ and thin eyebrows and thin upper lips characterizing ‘Type B’. Short stature and delayed bone age are also characteristic. Delayed dentition has been reported.¹⁶⁸ Work-up should include hand radiographs to assess for hypoplastic or absent phalanges on the fifth digit, renal ultrasound, ophthalmologic evaluation, hearing screen and cardiac evaluation to rule out cardiac malformations.

Whole exome sequencing has shown de novo autosomal dominant mutations in the SWItch/Sucrose (SWI/SNF) complex, which regulates chromatin structure and allows appropriate gene expression.¹⁶⁹ Since most cases are sporadic with two unaffected parents, an autosomal dominant inheritance mechanism is indistinguishable from autosomal recessive. Therefore, with an undetected mutation, parents had received an estimated recurrence risk of 10%.¹⁷⁰ With an identified de novo mutation in a child using DNA technology, the recurrence risk is reduced to 1–2%.¹⁷⁰ The differential diagnosis includes mosaic trisomy 9, brachymorphism-onychodysplasia-dysphalangism, deafness-onychodystrophy-osteodystrophy-mental retardation,¹⁶⁷ fetal hydantoin syndrome, fetal alcohol syndrome, and Cornelia de Lange syndrome. Patients with Coffin–Siris syndrome have been reported to have frequent upper respiratory and ear infections. Younger infants may have feeding problems. Anesthesia in children may be complicated by apnea.¹⁷¹

Mitochondrial disorders

Mitochondrial enzyme abnormalities are characterized by an unexplained association of symptoms with multiple involved organs that have no common embryologic origin or biologic function. An increasing number of involved organs and systems, appearing during the course of disease, is characteristic. In recent years, the causative mutations for many mitochondrial disorders have been described. Mitochondrial disorders have a heterogeneous group of findings, such as poor growth, vomiting, developmental delay, renal tubular dysfunction, and seizures. Therefore, the diagnosis is often delayed for many months. Over the past several years, cutaneous findings have begun to be recognized in mitochondrial diseases. The most common cutaneous findings in patients with mitochondrial disease include lipomas, alopecia, mottled pigmentation or poikiloderma, erythematous patches, hypertrichosis, and acrocyanosis.^{172,173} The alopecia seems to be related to hair shaft abnormalities, fractures (trichoschisis), twists (pili torti), and trichorrhexis nodosa. The mottled or reticulated pigmentation is most commonly in sun-exposed areas, such as the neck, dorsal arms, and forehead. Hypertrichosis has frequently been noted in Leigh syndrome. Neurologic features may include seizures, developmental delay, myoclonus, and ataxia. Skeletal muscle is involved, resulting in myopathy and hypotonia. Sideroblastic anemia and pancytopenia can be hematologic complications. The endocrine manifestations include hypoparathyroidism, growth deficiency, and diabetes mellitus. Cardiomyopathy and conduction defects are the cardiac manifestations. In addition, sensorineural deafness and lactic acidosis may also be present.¹⁷⁴ Mitochondria are ubiquitous and are the main organelle responsible for producing energy in cells. Several different mutations in the mitochondrial DNA (mtDNA) have been identified resulting in a variety of diseases, including Leigh syndrome (subacute necrotizing encephalopathy) and MELAS (mitochondrial encephalomyopathy, acidosis, and stroke-like episodes), and NARP (neurogenic muscle weakness, ataxia, and retinitis pigmentosa). Mitochondrial DNA mutations can be either inherited or acquired. Acquired mutations may be related to ultraviolet-induced damage and may play a role in aging.¹⁷⁵ Evaluation should include plasma lactate, pyruvate and ketone body levels, head CT or MRI, and muscle biopsy for histology and for genetic analysis of the mitochondrial DNA. Treatment is supportive.

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KEY REFERENCES

2. Tidyman WE, Rauken KA. The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. *Curr Opin Genet Dev* 2009;19(3):230–6.
5. National Institutes of Health Consensus Development Conference Statement. Neurofibromatosis. July 13–15, 1987, Bethesda, MD. *Neurofibromatosis* 1988;1(3):172–8.
10. Brems H, Chmara M, Sahbatou M, et al. Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. *Nat Genet* 2007;39(9):1120–6.
17. Digilio MC, Lepri F, Baban A, et al. RASopathies: Clinical Diagnosis in the First Year of Life. *Mol Syndromol* 2011;1(6):282–9.
27. Evans DG. Neurofibromatosis type 2 (NF-2): a clinical and molecular review. *Orphanet J Rare Dis* 2009;4:16.
29. Riviere JB, Mirzaa GM, O’Roak BJ, et al. De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. *Nat Genet* 2012;44(8):934–40.
46. Hyman MH, Whittemore VH. National Institutes of Health consensus conference: tuberous sclerosis complex. *Arch Neurol* 2000;57(5):662–5.
47. Jost CJ, Głowiczki P, Edwards WD, et al. Aortic aneurysms in children and young adults with tuberous sclerosis: report of two cases and review of the literature. *J Vasc Surg* 2001;33(3):639–42.
84. Smahi A, Courtois G, Rabia SH, et al. The NF-kappaB signalling pathway in human diseases: from incontinentia pigmenti to ectodermal dysplasias and immune-deficiency syndromes. *Hum Mol Genet* 2002;11(20):2371–5.
120. Callewaert B, Malfait F, Loeys B, et al. Ehlers-Danlos syndromes and Marfan syndrome. *Best Pract Res Clin Rheumatol* 2008;22(1):165–89.
135. Wang X, Reid Sutton V, Omar Peraza-Llanes J, et al. Mutations in X-linked PORCN, a putative regulator of Wnt signaling, cause focal dermal hypoplasia. *Nat Genet* 2007;39(7):836–8.

REFERENCES

1. Washington University. GeneReviews Medical Genetics Information Resource, Seattle 1993–2013. Available at: www.genereviews.org (Accessed February 2014).
2. Tidyman WE, Rauen KA. The RASopathies: developmental syndromes of Ras/MAPK pathway dysregulation. *Curr Opin Genet Dev* 2009;19(3):230–6.
3. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. *Am J Med Genet A* 2010;152A(2):327–32.
4. Lammert M, Friedman JM, Kluwe L, et al. Prevalence of neurofibromatosis 1 in German children at elementary school enrollment. *Arch Dermatol* 2005;141(1):71–4.
5. National Institutes of Health Consensus Development Conference Statement. Neurofibromatosis. July 13–15, 1987, Bethesda, MD. *Neurofibromatosis* 1988;1(3):172–8.
6. Viskochil DH. Neurofibromatosis type 1. In: Cassidy S, Allanson J, editors. *Management of genetic syndromes*. 2nd ed. Hoboken, NJ: John Wiley; 2005. p. 369–84.
7. Leppig KA, Kaplan P, Viskochil D, et al. Familial neurofibromatosis 1 microdeletions: cosegregation with distinct facial phenotype and early onset of cutaneous neurofibromata. *Am J Med Genet* 1997;73(2):197–204.
8. Hyman SL, Shores A, North KN. The nature and frequency of cognitive deficits in children with neurofibromatosis type 1. *Neurology* 2005;65(7):1037–44.
9. Martin GA, Viskochil D, Bollag G, et al. The GAP-related domain of the neurofibromatosis type 1 gene product interacts with ras p21. *Cell* 1990;63(4):843–9.
10. Brems H, Chmara M, Sahbatou M, et al. Germline loss-of-function mutations in SPRED1 cause a neurofibromatosis 1-like phenotype. *Nat Genet* 2007;39(9):1120–6.
11. Messiaen L, Yao S, Brems H, et al. Clinical and mutational spectrum of neurofibromatosis type 1-like syndrome. *JAMA* 2009;302(19):2111–18.
12. Tartaglia M, Gelb BD. Germ-line and somatic PTPN11 mutations in human disease. *Eur J Med Genet* 2005;48(2):81–96.
13. Mendez HM, Opitz JM. Noonan syndrome: a review. *Am J Med Genet* 1985;21(3):493–506.
14. Roberts AE, Allanson JE, Tartaglia M, et al. Noonan syndrome. *Lancet* 2013;381(9863):333–42.
15. Cordeddu V, Di Schiavi E, Pennacchio LA, et al. Mutation of SHOC2 promotes aberrant protein N-myristoylation and causes Noonan-like syndrome with loose anagen hair. *Nat Genet* 2009;41(9):1022–6.
16. Digilio MC, Conti E, Sarkozy A, et al. Grouping of multiple-lentiginos/LEOPARD and Noonan syndromes on the PTPN11 gene. *Am J Hum Genet* 2002;71(2):389–94.
17. Digilio MC, Lepri F, Baban A, et al. RASopathies: Clinical Diagnosis in the First Year of Life. *Mol Syndromol* 2011;1(6):282–9.
18. Siegel DH, McKenzie J, Frieden IJ, et al. Dermatological findings in 61 mutation-positive individuals with cardiofaciocutaneous syndrome. *Br J Dermatol* 2011;164(3):521–9.
19. Rodriguez-Viciana P, Tetsu O, Tidyman WE, et al. Germline mutations in genes within the MAPK pathway cause cardio-facio-cutaneous syndrome. *Science* 2006;311(5765):1287–90.
20. Allanson JE, Anneren G, Aoki Y, et al. Cardio-facio-cutaneous syndrome: does genotype predict phenotype? *Am J Med Genet C Semin Med Genet* 2011;157(2):129–35.
21. Estep AL, Tidyman WE, Teitell MA, et al. HRAS mutations in Costello syndrome: detection of constitutional activating mutations in codon 12 and 13 and loss of wild-type allele in malignancy. *Am J Med Genet A* 2006;140(1):8–16.
22. Digilio MC, Sarkozy A, Capolino R, et al. Costello syndrome: clinical diagnosis in the first year of life. *Eur J Pediatr* 2008;167(6):621–8.
23. Siegel DH, Mann JA, Krol AL, et al. Dermatological phenotype in Costello syndrome: consequences of Ras dysregulation in development. *Br J Dermatol* 2012;166(3):601–7.
24. Revencu N, Boon LM, Mulliken JB, et al. Parkes Weber syndrome, vein of Galen aneurysmal malformation, and other fast-flow vascular anomalies are caused by RASA1 mutations. *Hum Mutat* 2008;29(7):959–65.
25. Miyakawa T, Kamada N, Kobayashi T, et al. Neurofibromatosis type 2 in an infant with multiple plexiform schwannomas as first symptom. *J Dermatol* 2007;34(1):60–4.
26. Evans DG, Baser ME, O'Reilly B, et al. Management of the patient and family with neurofibromatosis 2: a consensus conference statement. *Br J Neurosurg* 2005;19(1):5–12.
27. Evans DG. Neurofibromatosis type 2 (NF-2): a clinical and molecular review. *Orphanet J Rare Dis* 2009;4:16.
28. Craiglow BG, Ko CJ, Antaya RJ. Two cases of hemihyperplasia-multiple lipomatosis syndrome and review of asymmetric hemihyperplasia syndromes. *Pediatr Dermatol* 2013; Mar 5, doi: 10.1111/pde.12071 [Epub ahead of print].
29. Riviere JB, Mirzaa GM, O'Roak BJ, et al. De novo germline and postzygotic mutations in AKT3, PIK3R2 and PIK3CA cause a spectrum of related megalencephaly syndromes. *Nat Genet* 2012;44(8):934–40.
30. Brasseco MS, Valera ET, Becker AP, et al. Low-grade astrocytoma in a child with encephalocraniocutaneous lipomatosis. *J Neurooncol* 2010;96(3):437–41.
31. Moog U. Encephalocraniocutaneous lipomatosis. *J Med Genet* 2009;46(11):721–9.
32. Tatton-Brown K, Rahman N. Sotos syndrome. *Eur J Hum Genet* 2007;15(3):264–71.
33. Fickie MR, Lapunzina P, Gentile JK, et al. Adults with Sotos syndrome: review of 21 adults with molecularly confirmed NSD1 alterations, including a detailed case report of the oldest person. *Am J Med Genet A* 2011;155A(9):2105–11.
34. Cohen MM, Neri G, Weksberg R. Proteus Syndrome. In: Michael M, Cohen J, Neri G, Weksberg R, editors. *Overgrowth syndromes*. New York: Oxford University Press; 2002. p. 75–110.
35. Blumenthal GM, Dennis PA. PTEN hamartoma tumor syndromes. *Eur J Hum Genet* 2008;16(11):1289–300.
36. Korkolopoulou P, Levidou G, Trigka EA, et al. A comprehensive immunohistochemical and molecular approach to the PI3K/AKT/mTOR (phosphoinositide 3-kinase/v-akt murine thymoma viral oncogene/mammalian target of rapamycin) pathway in bladder urothelial carcinoma. *BJU Int* 2012;110(11 Pt C):E1237–48.
37. Webb DW, Clarke A, Fryer A, et al. The cutaneous features of tuberous sclerosis: a population study. *Br J Dermatol* 1996;135(1):1–5.
38. Vanderhooft SL, Francis JS, Pagon RA, et al. Prevalence of hypopigmented macules in a healthy population. *J Pediatr* 1996;129(3):355–61.
39. Sidenvall R, Eeg-Olofsson O. Epidemiology of infantile spasms in Sweden. *Epilepsia* 1995;36(6):572–4.
40. Webb DW, Osborne JP. Tuberous sclerosis. *Arch Dis Child* 1995;72(6):471–4.
41. Bosi G, Lintermans JP, Pellegrino PA, et al. The natural history of cardiac rhabdomyoma with and without tuberous sclerosis. *Acta Paediatr* 1996;85(8):928–31.
42. Smith HC, Watson GH, Patel RG, et al. Cardiac rhabdomyomata in tuberous sclerosis: their course and diagnostic value. *Arch Dis Child* 1989;64(2):196–200.
43. Roach ES, DiMario FJ, Kandt RS, et al. Tuberous Sclerosis Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. *J Child Neurol* 1999;14(6):401–7.
44. Kwiatkowski DJ. Tuberous sclerosis: from tubers to mTOR. *Ann Hum Genet* 2003;67(Pt 1):87–96.
45. Darling TN, Skarulis MC, Steinberg SM, et al. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. *Arch Dermatol* 1997;133(7):853–7.
46. Hyman MH, Whittemore VH. National Institutes of Health consensus conference: tuberous sclerosis complex. *Arch Neurol* 2000;57(5):662–5.
47. Jost CJ, Głowiczki P, Edwards WD, et al. Aortic aneurysms in children and young adults with tuberous sclerosis: report of two cases and review of the literature. *J Vasc Surg* 2001;33(3):639–42.
48. Papadavid E, Markey A, Bellaney G, et al. Carbon dioxide and pulsed dye laser treatment of angiofibromas in 29 patients with tuberous sclerosis. *Br J Dermatol* 2002;147(2):337–42.
49. Salido R, Garnacho-Saucedo G, Cuevas-Asencio I, et al. Sustained clinical effectiveness and favorable safety profile of topical sirolimus for tuberous sclerosis – associated facial angiofibroma. *J Eur Acad Dermatol Venereol* 2012;26(10):1315–18.
50. DeKlotz CM, Ogram AE, Singh S, et al. Dramatic improvement of facial angiofibromas in tuberous sclerosis with topical rapamycin: optimizing a treatment protocol. *Arch Dermatol* 2011;147(9):1116–17.
51. Lindhurst MJ, Sapp JC, Teer JK, et al. A mosaic activating mutation in AKT1 associated with the Proteus syndrome. *N Engl J Med* 2011;365(7):611–19.
52. Turner JT, Cohen MM Jr, Biesecker LG. Reassessment of the Proteus syndrome literature: application of diagnostic criteria to published cases. *Am J Med Genet A* 2004;130A(2):111–22.
53. Twede JV, Turner JT, Biesecker LG, et al. Evolution of skin lesions in Proteus syndrome. *J Am Acad Dermatol* 2005;52(5):834–8.

54. Beachkofsky TM, Sapp JC, Biesecker LG, et al. Progressive overgrowth of the cerebriform connective tissue nevus in patients with Proteus syndrome. *J Am Acad Dermatol* 2010;63(5):799–804.
55. Newman B, Urbach AH, Orenstein D, et al. Proteus syndrome: emphasis on the pulmonary manifestations. *Pediatr Radiol* 1994;24(3):189–93.
56. Slavotinek AM, Vacha SJ, Peters KF, et al. Sudden death caused by pulmonary thromboembolism in Proteus syndrome. *Clin Genet* 2000;58(5):386–9.
57. Biesecker LG. Proteus syndrome. In: Cassidy SB, Allanson JE, editors. *Management of genetic syndromes*. Hoboken, NJ: Wiley; 2005. p. 449–56.
58. Sapp JC, Turner JT, van de Kamp JM, et al. Newly delineated syndrome of congenital lipomatous overgrowth, vascular malformations, and epidermal nevi (CLOVE syndrome) in seven patients. *Am J Med Genet A* 2007;143A(24):2944–58.
59. Biesecker LG, Peters KF, Darling TN, et al. Clinical differentiation between Proteus syndrome and hemihyperplasia: description of a distinct form of hemihyperplasia. *Am J Med Genet* 1998;79(4):311–18.
60. Martinez-Glez V, Romanelli V, Mori MA, et al. Macrocephaly-capillary malformation: Analysis of 13 patients and review of the diagnostic criteria. *Am J Med Genet A* 2010;152A(12):3101–6.
61. Conwat RL, Pressman BD, Dobyns WB, et al. Neuroimaging findings in macrocephaly-capillary malformation: a longitudinal study of 17 patients. *Am J Med Genet A* 2007;143A:2981–3008.
62. Lindhurst MJ, Parker VE, Payne F, et al. Mosaic overgrowth with fibroadipose hyperplasia is caused by somatic activating mutations in PIK3CA. *Nat Genet* 2012;44(8):928–33.
63. Caux F, Plauchu H, Chibon F, et al. Segmental overgrowth, lipomatosis, arteriovenous malformation and epidermal nevus (SOLAMEN) syndrome is related to mosaic PTEN nullizygosity. *Eur J Hum Genet* 2007;15(7):767–73.
64. Alomari AI. Comments on the diagnosis and management of CLOVES syndrome. *Pediatr Dermatol* 2011;28(2):215–16.
65. Kurek KC, Luks VL, Ayturk UM, et al. Somatic mosaic activating mutations in PIK3CA cause CLOVES syndrome. *Am J Hum Genet* 2012;90(6):1108–15.
66. Harit D, Aggarwal A. CLOVE syndrome with nevus unis lateris: report of a case. *Pediatr Dermatol* 2010;27(3):311–12.
67. Amary MF, Damato S, Halai D, et al. Ollier disease and Maffucci syndrome are caused by somatic mosaic mutations of IDH1 and IDH2. *Nat Genet* 2011;43(12):1262–5.
68. Biesecker LG, Sapp JC. Proteus syndrome. In: Pagon RA, Bird TD, Dolan CR, et al, editors. *GeneReviews™* [Internet]. Seattle, WA: University of Washington; 1993–2012. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK99495/>. (Accessed February 2014).
69. Dempsey-Robertson M, Wilkes D, Stall A, et al. Incidence of abdominal tumors in syndromic and idiopathic hemihypertrophy/isolated hemihyperplasia. *J Pediatr Orthop* 2012;32(3):322–6.
70. Choufani S, Shuman C, Weksberg R. Beckwith-Wiedemann syndrome. *Am J Med Genet C Semin Med Genet* 2010;154C(3):343–54.
71. Ishida M, Moore GE. The role of imprinted genes in humans. *Mol Aspects Med* 2012;34(4):826–40.
72. Garavelli L, Gargano G, Simonte G, et al. Simpson-Golabi-Beckel syndrome type 1 in a 27-week macrosomic preterm newborn: the diagnostic value of rib malformations and index nail and finger hypoplasia. *Am J Med Genet A* 2012;158A(9):2245–9.
73. Chen CP. Prenatal findings and the genetic diagnosis of fetal overgrowth disorders: Simpson-Golabi-Beckel syndrome, Sotos syndrome, and Beckwith-Wiedemann syndrome. *Taiwan J Obstet Gynecol* 2012;51(2):186–91.
74. Nicita F, Ruggieri M, Polizzi A, et al. Seizures and epilepsy in Sotos syndrome: analysis of 19 Caucasian patients with long-term follow-up. *Epilepsia* 2012;53(6):e102–5.
75. Clarke A, Phillips DI, Brown R, et al. Clinical aspects of X-linked hypohidrotic ectodermal dysplasia. *Arch Dis Child* 1987;62(10):989–96.
76. Scaling skin in the neonate: a clue to the early diagnosis of X-linked hypohidrotic ectodermal dysplasia (Christ-Siemens-Touraine syndrome). The Executive and Scientific Advisory Boards of the National Foundation for Ectodermal Dysplasias, Mascoutah, IL. *J Pediatr* 1989;114(4 Pt 1):600–2.
77. Mikkola ML, Thesleff I. Ectodysplasin signaling in development. *Cytokine Growth Factor Rev* 2003;14(3–4):211–24.
78. Headon DJ, Emmal SA, Ferguson BM, et al. Gene defect in ectodermal dysplasia implicates a death domain adapter in development. *Nature* 2001;414(6866):913–16.
79. van Bokhoven H, Hamel BC, Bamshad M, et al. p63 Gene mutations in eec syndrome, limb-mammary syndrome, and isolated split hand-split foot malformations suggest a genotype-phenotype correlation. *Am J Hum Genet* 2001;69(3):481–92.
80. Brunner HG, Hamel BC, Van Bokhoven H. The p63 gene in EEC and other syndromes. *J Med Genet* 2002;39(6):377–81.
81. Dhanrajani PJ, Jiffry AO. Management of ectodermal dysplasia: a literature review. *Dent Update* 1998;25(2):73–5.
82. Zonana J, Elder ME, Schneider LC, et al. A novel X-linked disorder of immune deficiency and hypohidrotic ectodermal dysplasia is allelic to incontinentia pigmenti and due to mutations in IKK-gamma (NEMO). *Am J Hum Genet* 2000;67(6):1555–62.
83. Kawai T, Nishikomori R, Izawa K, et al. Frequent somatic mosaicism of NEMO in T cells of patients with X-linked anhidrotic ectodermal dysplasia with immunodeficiency. *Blood* 2012;119(23):5458–66.
84. Smahi A, Courtois G, Rabia SH, et al. The NF-kappaB signalling pathway in human diseases: from incontinentia pigmenti to ectodermal dysplasias and immune-deficiency syndromes. *Hum Mol Genet* 2002;11(20):2371–5.
85. Carney RG. Incontinentia pigmenti. A world statistical analysis. *Arch Dermatol* 1976;112(4):535–42.
86. Donnai D. Incontinentia pigmenti. In: Cassidy SB, Allanson JE, editors. *Management of genetic syndromes*. Hoboken, NJ: Wiley; 2005. p. 309–14.
87. Goldberg MF, Custis PH. Retinal and other manifestations of incontinentia pigmenti (Bloch-Sulzberger syndrome). *Ophthalmology* 1993;100(11):1645–54.
88. Wald KJ, Mehta MC, Katsumi O, et al. Retinal detachments in incontinentia pigmenti. *Arch Ophthalmol* 1993;111(5):614–17.
89. Landy SJ, Donnai D. Incontinentia pigmenti (Bloch-Sulzberger syndrome). *J Med Genet* 1993;30(1):53–9.
90. Meuwissen ME, Mancini GM. Neurological findings in incontinentia pigmenti; a review. *Eur J Med Genet* 2012;55(5):323–31.
91. Smahi A, Courtois G, Vabres P, et al. Genomic rearrangement in NEMO impairs NF-kappaB activation and is a cause of incontinentia pigmenti. The International Incontinentia Pigmenti (IP) Consortium. *Nature* 2000;405(6785):466–72.
92. Clouston HR. A hereditary ectodermal dystrophy. *Can Med Assoc J* 1929;21(1):18–31.
93. Smith SB, Ervin JW. What is your diagnosis? Hidrotic ectodermal dysplasia. *Cutis* 2003;71(3):190, 224–225.
94. Lamartine J, Munhoz Essensfelder G, Kibar Z, et al. Mutations in GJB6 cause hidrotic ectodermal dysplasia. *Nat Genet* 2000;26(2):142–4.
95. Itin PH, Fistarol SK. Ectodermal dysplasias. *Am J Med Genet C Semin Med Genet* 2004;131C(1):45–51.
96. Brunner HG, Hamel BC, Bokhoven Hv H. P63 gene mutations and human developmental syndromes. *Am J Med Genet* 2002;112(3):284–90.
97. Rinne T, Brunner HG, van Bokhoven H. p63-associated disorders. *Cell Cycle* 2007;6(3):262–8.
98. Koster MI. p63 in skin development and ectodermal dysplasias. *J Invest Dermatol* 2010;130(10):2352–8.
99. Guerrini L, Costanzo A, Merlo GR. A symphony of regulations centered on p63 to control development of ectoderm-derived structures. *J Biomed Biotechnol* 2011;2011:864904.
100. Hay RJ, Wells RS. The syndrome of ankyloblepharon, ectodermal defects and cleft lip and palate: an autosomal dominant condition. *Br J Dermatol* 1976;94(3):277–89.
101. Vanderhooft SL, Stephan MJ, Sybert VP. Severe skin erosions and scalp infections in AEC syndrome. *Pediatr Dermatol* 1993;10(4):334–40.
102. Buss PW, Hughes HE, Clarke A. Twenty-four cases of the EEC syndrome: clinical presentation and management. *J Med Genet* 1995;32(9):716–23.
103. Roelfsema NM, Cobben JM. The EEC syndrome: a literature study. *Clin Dysmorphol* 1996;5(2):115–27.
104. Fosko SW, Stenn KS, Bologna JL. Ectodermal dysplasias associated with clefting: significance of scalp dermatitis. *J Am Acad Dermatol* 1992;27(2 Pt 1):249–56.
105. Rodini ES, Richieri-Costa A. EEC syndrome: report on 20 new patients, clinical and genetic considerations. *Am J Med Genet* 1990;37(1):42–53.
106. McNab AA, Potts MJ, Welham RA. The EEC syndrome and its ocular manifestations. *Br J Ophthalmol* 1989;73(4):261–4.
107. Spitz JL. Disorders of hair and nails. In: Spitz JL, editor. *Nodular dermatoses: a clinical guide to genetic skin disorders*. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 273–301.
108. Celli J, Duijff P, Hamel BC, et al. Heterozygous germline mutations in the p53 homolog p63 are the cause of EEC syndrome. *Cell* 1999;99(2):143–53.
109. Ringpfeil F. Selected disorders of connective tissue: pseudoxanthoma elasticum, cutis laxa,

- and lipoid proteinosis. *Clin Dermatol* 2005; 23(1):41–6.
110. Damkier A, Brandrup F, Starklint H. Cutis laxa: autosomal dominant inheritance in five generations. *Clin Genet* 1991;39(5):321–9.
 111. Paller AS, Mancini AJ. Hereditary disorders of the dermis. In: Paller AS, Mancini AJ, editors. *Hurwitz clinical pediatric dermatology*. 3rd ed. Philadelphia: Elsevier; 2006. p. 129–44.
 112. Hwang ST, Williams ML, McCalmont TH, et al. Sweet's syndrome leading to acquired cutis laxa (Marshall's syndrome) in an infant with alpha 1-antitrypsin deficiency. *Arch Dermatol* 1995;131(10):1175–7.
 113. Bogart MM, Arnold HE, Greer KE. Prune-belly syndrome in two children and review of the literature. *Pediatr Dermatol* 2006;23(4):342–5.
 114. Uitto J. Cutis laxa: Clinical pearls. In: Spitz JL, editor. *Genodermatoses: A clinical guide to genetic skin disorders*. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 142–3.
 115. Kaler SG. Diagnosis and therapy of Menkes syndrome, a genetic form of copper deficiency. *Am J Clin Nutr* 1998;67(5 Suppl):1029S–34S.
 116. Zampatti S, Castori M, Fischer B, et al. De Barsy Syndrome: a genetically heterogeneous autosomal recessive cutis laxa syndrome related to P5CS and PYCR1 dysfunction. *Am J Med Genet A* 2012;158A(4):927–31.
 117. Wenstrup RJ, Hoechstetter LB. Ehlers-Danlos syndromes. In: Cassidy SB, Allanson JE, editors. *Management of genetic syndromes*. Hoboken, NJ: Wiley; 2005. p. 211–23.
 118. Beighton P, de Paepe A, Danks D, et al. International nosology of heritable disorders of connective tissue. Berlin, 1986. *Am J Med Genet* 1988;29(3):581–94.
 119. Beighton P, De Paepe A, Steinmann B, et al. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). *Am J Med Genet* 1998;77(1):31–7.
 120. Callewaert B, Malfait F, Loeys B, et al. Ehlers-Danlos syndromes and Marfan syndrome. *Best Pract Res Clin Rheumatol* 2008;22(1):165–89.
 121. Mayer K, Kennerknecht I, Steinmann B. Clinical utility gene card for: Ehlers-Danlos syndrome types I–VII and variants – update 2012. *Eur J Hum Genet* 2013;21(1).
 122. Lind J, Wallenburg HC. Pregnancy and the Ehlers-Danlos syndrome: a retrospective study in a Dutch population. *Acta Obstet Gynecol Scand* 2002;81(4):293–300.
 123. Elsas LJ 2nd, Miller RL, Pinnell SR, et al. Inherited human collagen lysyl hydroxylase deficiency: ascorbic acid response. *J Pediatr* 1978;92(3):378–84.
 124. Uitto J. Ehlers-Danlos: Clinical pearls. In: Spitz JL, editor. *Genodermatoses: A clinical guide to genetic skin disorders*. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 136.
 125. Skaria A, Feldmann R, Hauser C. [The clinical spectrum of focal dermal hypoplasia]. *Hautarzt* 1995;46(11):779–84.
 126. Terezhalmay GT, Moore WS, Bsoul SA, et al. Focal dermal hypoplasia (Goltz-Gorlin syndrome). *Quintessence Int* 2002;33(9):706–7.
 127. Hall EH, Terezhalmay GT. Focal dermal hypoplasia syndrome. Case report and literature review. *J Am Acad Dermatol* 1983;9(3):443–51.
 128. Ayme S, Fraser FC. Possible examples of the Goltz syndrome (focal dermal hypoplasia) without linear areas of skin hypoplasia. *Birth Defects Orig Artic Ser* 1982;18(3B):59–65.
 129. Goltz RW. Focal dermal hypoplasia syndrome. An update. *Arch Dermatol* 1992;128(8):1108–11.
 130. Howell JB, Reynolds J. Osteopathia striata. A diagnostic osseous marker of focal dermal hypoplasia. *Trans St Johns Hosp Dermatol Soc* 1974;60(2):178–82.
 131. Happle R, Lenz W. Striation of bones in focal dermal hypoplasia: manifestation of functional mosaicism? *Br J Dermatol* 1977;96(2):133–5.
 132. Samejima N, Ito S, Nakajima S, et al. Omphalocele and focal dermal hypoplasia. *Z Kinderchir* 1981;34(3):284–9.
 133. Han XY, Wu SS, Conway DH, et al. Truncus arteriosus and other lethal internal anomalies in Goltz syndrome. *Am J Med Genet* 2000;90(1):45–8.
 134. Grzeschik KH, Bornholdt D, Oeffner F, et al. Deficiency of PORCN, a regulator of Wnt signaling, is associated with focal dermal hypoplasia. *Nat Genet* 2007;39(7):833–5.
 135. Wang X, Reid Sutton V, Omar Peraza-Llanes J, et al. Mutations in X-linked PORCN, a putative regulator of Wnt signaling, cause focal dermal hypoplasia. *Nat Genet* 2007;39(7):836–8.
 136. Groesser L, Herschberger E, Ruetten A, et al. Postzygotic HRAS and KRAS mutations cause nevus sebaceous and Schimmelpenning syndrome. *Nat Genet* 2012;44(7):783–7.
 137. Hafner C, Toll A, Gantner S, et al. Keratinocytic epidermal nevi are associated with mosaic RAS mutations. *J Med Genet* 2012;49(4):249–53.
 138. al-Gazali LI, Mueller RF, Caine A, et al. Two 46,XX,t(X;Y) females with linear skin defects and congenital microphthalmia: a new syndrome at Xp22.3. *J Med Genet* 1990;27(1):59–63.
 139. Happle R, Daniels O, Koopman RJ. MIDAS syndrome (microphthalmia, dermal aplasia, and sclerocornea): an X-linked phenotype distinct from Goltz syndrome. *Am J Med Genet* 1993;47(5):710–13.
 140. Wimplinger I, Morleo M, Rosenberger G, et al. Mutations of the mitochondrial holocytochrome c-type synthase in X-linked dominant microphthalmia with linear skin defects syndrome. *Am J Hum Genet* 2006;79(5):878–89.
 141. Lowenstein EJ, Kim KH, Glick SA. Turner's syndrome in dermatology. *J Am Acad Dermatol* 2004;50(5):767–76.
 142. Kaplowitz PB, Chernausk SD, Horn JA. Fingernail angle in girls with Ullrich-Turner syndrome. *Am J Med Genet* 1993;46(5):570–3.
 143. Larralde M, Gardner SS, Torrado MV, et al. Lymphedema as a postulated cause of cutis verticis gyrata in Turner syndrome. *Pediatr Dermatol* 1998;15(1):18–22.
 144. Lemli L, Smith DW. The Xo Syndrome. A Study of the Differentiated Phenotype in 25 Patients. *J Pediatr* 1963;63:577–88.
 145. Bataille V, Snieder H, MacGregor AJ, et al. Genetics of risk factors for melanoma: an adult twin study of nevi and freckles. *J Natl Cancer Inst* 2000;92(6):457–63.
 146. Gibbs P, Brady BM, Gonzalez R, et al. Nevi and melanoma: lessons from Turner's syndrome. *Dermatology* 2001;202(1):1–3.
 147. Sybert VP. Turner Syndrome. In: Cassidy SB, Allanson JL, editors. *Management of genetic syndromes*. Hoboken, NJ: Wiley; 2005. p. 589–606.
 148. Sybert VP, McCauley E. Turner's syndrome. *N Engl J Med* 2004;351(12):1227–38.
 149. Ranke MB, Saenger P. Turner's syndrome. *Lancet* 2001;358(9278):309–14.
 150. De Sanctis V, Tosetto I, Iughetti L, et al. The SHOX gene and the short stature. Roundtable on diagnosis and treatment of short stature due to SHOX haploinsufficiency: how genetics, radiology and anthropometry can help the pediatrician in the diagnostic process Padova (April 20th, 2011). *Pediatr Endocrinol Rev* 2012;9(4):727–33.
 151. Pinsker JE. Clinical review: Turner syndrome: updating the paradigm of clinical care. *J Clin Endocrinol Metab* 2012;97(6):E994–1003.
 152. Lejeune J, Turpin R, Gautier M. [Mongolism; a chromosomal disease (trisomy)]. *Bull Acad Natl Med* 1959;143(11–12):256–65.
 153. Hattori M, Fujiyama A, Taylor TD, et al. The DNA sequence of human chromosome 21. *Nature* 2000;405(6784):311–19.
 154. Burch JM, Weston WL, Rogers M, et al. Cutaneous pustular leukemoid reactions in trisomy 21. *Pediatr Dermatol* 2003;20(3):232–7.
 155. Scherbenko JM, Benson PM, Rotchford JP, et al. Cutaneous and ocular manifestations of Down syndrome. *J Am Acad Dermatol* 1990;22(5 Pt 2):933–8.
 156. Marmon S, De Souza A, Strober BE. Psoriasis and Down syndrome: a report of three cases and a potential pathophysiologic link. *Dermatol Online J* 2012;18(6):13.
 157. Carey J. Trisomy 18 and trisomy 13 syndromes. In: Cassidy SB, Allanson JL, editors. *Management of genetic syndromes*. 2nd ed. Hoboken, NJ: Wiley; 2005. p. 555–68.
 158. Munoz RM, Santos AC, Graziadio C, et al. Cerebello-trigeminal-dermal dysplasia (Gomez-Lopez-Hernandez syndrome): description of three new cases and review. *Am J Med Genet* 1997;72(1):34–9.
 159. Sukhudyay B, Jaladyan V, Melikyan G, et al. Gomez-Lopez-Hernandez syndrome: reappraisal of the diagnostic criteria. *Eur J Pediatr* 2010;169(12):1523–8.
 160. Poretti A, Bartholdi D, Gobara S, et al. Gomez-Lopez-Hernandez syndrome: an easily missed diagnosis. *Eur J Med Genet* 2008;51(3):197–208.
 161. Gomez MR. Cerebello-trigemino-dermal dysplasia. In: Gomez MR, editor. *Neurocutaneous diseases*. New York: Raven Press; 1987. p. 145–8.
 162. Mass E. A review of the oro-dento-facial characteristics of hereditary sensory and autonomic neuropathy type III (familial dysautonomia). *Spec Care Dentist* 2012;32(1):15–20.
 163. Gold-von Simson G, Axelrod FB. Familial dysautonomia: update and recent advances. *Curr Probl Pediatr Adolesc Health Care* 2006;36(6):218–37.
 164. Lerner BH. When diseases disappear – the case of familial dysautonomia. *N Engl J Med* 2009;361(17):1622–5.
 165. Axelrod FB, Porges RF, Sein ME. Neonatal recognition of familial dysautonomia. *J Pediatr* 1987;110(6):946–8.
 166. Axelrod FB, Liebes L, Gold-Von Simson G, et al. Kinetin improves IKBKAP mRNA splicing in patients with familial dysautonomia. *Pediatr Res* 2011;70(5):480–3.
 167. Schrier SA, Bodurtha JN, Burton B, et al. The Coffin-Siris syndrome: a proposed diagnostic approach and assessment of 15 overlapping

- cases. *Am J Med Genet A* 2012;158A(8):1865–76.
168. Fleck BJ, Pandya A, Vanner L, et al. Coffin-Siris syndrome: review and presentation of new cases from a questionnaire study. *Am J Med Genet* 2001;99(1):1–7.
 169. Tsurusaki Y, Okamoto N, Ohashi H, et al. Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome. *Nat Genet* 2012;44(4):376–8.
 170. Santen GW, Aten E, Sun Y, et al. Mutations in SWI/SNF chromatin remodeling complex gene ARID1B cause Coffin-Siris syndrome. *Nat Genet* 2012;44(4):379–80.
 171. Silvani P, Camporesi A, Zoia E, et al. Anesthetic management in a child with Coffin-Siris syndrome. *Paediatr Anaesth* 2004;14(8):698–700.
 172. Bodemer C, Rotig A, Rustin P, et al. Hair and skin disorders as signs of mitochondrial disease. *Pediatrics* 1999;103(2):428–33.
 173. Flynn MK, Wee SA, Lane AT. Skin manifestations of mitochondrial DNA syndromes: case report and review. *J Am Acad Dermatol* 1998;39(5 Pt 2):819–23.
 174. Birch-Machin MA. Mitochondria and skin disease. *Clin Exp Dermatol* 2000;25(2):141–6.
 175. Pang CY, Lee HC, Yang JH, et al. Human skin mitochondrial DNA deletions associated with light exposure. *Arch Biochem Biophys* 1994;312(2):534–8.

Neonatal Mucous Membrane Disorders

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Introduction

Examination of the mucous membranes is an important, yet often overlooked, part of the neonatal evaluation. This chapter discusses abnormal cutaneous findings of the oral, genital, and ocular systems. Many of these abnormalities provide important clues to the diagnosis of underlying disease and/or developmental syndromes in the newborn infant.^{1,2}

Disorders of the oral mucous membranes

DEVELOPMENTAL DEFECTS, GROWTHS, AND HAMARTOMAS

See Table 30.1.

Bohn's nodules

Bohn's nodules are multiple, small cystic structures found along the lingual gum margins and lateral palate (Fig. 30.1). These lesions are commonly found in up to 85% of newborn infants. Bohn's nodules most likely develop from epithelial remnants of salivary gland tissue or from remnants of the dental lamina. However, some authors refute this idea because mucinous glands are rarely found on the lateral edge of the gingival margins. Bohn's nodules are felt to be asymptomatic and occur more often in full-term infants than in premature newborns.³⁻⁶ Treatment is unnecessary as involution or shedding usually occurs.

Congenital epulis

A congenital epulis is a rare, benign tumor of the newborn. Clinically, the lesion is a solitary soft nodule, measuring from 1 to several millimeters in diameter, and often pedunculated. The lesion represents a hamartoma of the alveolar ridge.⁷ The epulis forms over the gingival margin, most frequently along the anterior maxillary ridge or the incisor/canine.^{8,9} Lesions on the alveolar ridge occur twice as often as on the maxilla.⁷ Female infants are more often affected, with a female to male ratio of 3:2. Fetal ovarian estrogen levels were originally thought to account for this predominance, but this concept has been challenged.¹⁰ Currently, there is no known cause of these lesions and no teratogenic or genetic association has been reported.

Histologic examination shows tightly packed granular cells surrounded by a prominent fibrovascular network. The absence of pseudoepitheliomatous hyperplasia and neural elements differentiates the epulis from a granular cell myoblastoma.

Lesions may regress spontaneously over time. However, difficulties with feeding and respiration can occur with large or multiple lesions.¹¹ Simple excision is curative; recurrences have not been reported.

Congenital ranula

A congenital ranula is a very rare type of mucocoele that results from an obstructed, imperforate, or atretic sublingual or submandibular salivary gland duct. Lesions are found specifically on the anterior floor of the mouth, lateral to the lingual frenulum. The overlying mucosa may be normal in color or have a translucent blue hue. These retention cysts are asymptomatic.

Ranulae may resemble mucous retention cysts, dermoid cysts, or cystic hygromas. Differentiation of a ranula from a mucous retention cyst can be confirmed only by histopathologic examination. Although the mucous retention cyst is a true cyst lined by epithelium, the ranula is a pseudocyst. Ranulae may rupture spontaneously during feeding and sucking; however, lesions that enlarge over time should be treated early with marsupialization with packing. In some cases, failure to operate may lead to sialadenitis. If surgery is warranted, the risk of recurrence postoperatively is minimal.^{12,13}

Epstein's pearls

Epstein's pearls are benign cystic lesions that occur along the median palatal raphe, most commonly at the junction of the hard and soft palates (Fig. 30.2). Lesions are multiple and small, ranging in size from less than a millimeter to several millimeters in diameter. The overall appearance is similar to that of Bohn's nodules, but the location and etiology make this a distinct entity. Epstein's pearls are common, occurring in 60–85% of newborn infants. Japanese newborns are most commonly affected (up to 92%), followed by Caucasians and African-Americans.^{4,6,14}

Epstein's pearls are epidermal inclusion cysts formed during the fusion of the soft and hard palates, and contain desquamated keratin within their lumina. They are considered the counterpart of milia, which are commonly seen on the faces of neonates. No therapy is indicated, as most lesions rupture spontaneously within the first few weeks to months of life.^{3,4,14}

Eruption cysts

An eruption cyst (or eruption hematoma) is a circumscribed fluctuant swelling that develops over the site of an erupting tooth (Fig. 30.3). Lesions in the newborn may occur secondary to natal or neonatal teeth, but these cysts are more commonly associated with the eruption of deciduous or permanent teeth. Eruption cysts most commonly develop on the alveolar ridge of the maxilla or mandible. Size varies with the type of tooth overlaid, but most lesions are approximately 0.6 cm in diameter. The surface of the cyst may appear flesh-colored or have a bluish-red to blue-black color if the cyst cavity contains blood. Although removal of the tissue overlying the tooth may aid in its eruption, most eruption cysts resolve spontaneously within several weeks.¹⁵

TABLE
30.1

Benign papular and nodular lesions of the oral cavity

Lesion	Morphology	Most common location
Bohn's nodules	Multiple, small cysts	Gingival margin, lateral palate
Congenital epulis	Pedunculated, soft nodule from 1 mm to several cm in diameter	Gingival margin
Congenital ranula	Translucent, firm papule or nodule	Anterior floor of mouth, lateral to lingual frenulum
Epstein's pearls	Multiple, tiny (< few mm) cysts	Median palatal raphe
Eruption cysts	Circumscribed, fluctuant swelling; may have bluish-red to black surface if hemorrhage has occurred	Alveolar ridge of mandible or maxilla
Granular cell tumor	Small (<3 cm in diameter), firm, flesh-colored nodule	Tongue
Hemangioma	Red to blue, soft to semi-firm nodule	Lip, buccal mucosa, palate
Lymphangioma	Translucent papules or nodule	Tongue
Neurofibroma	Soft, flesh-colored nodule	Tongue
Nevus sebaceus	Verrucous yellow plaques	Lip, gingiva
Venous malformation	Bluish, compressible nodule; often intermittently painful	Oropharynx
Verrucae	Papillomatous white or pink papules	Lip, tongue, palate
White sponge nevus	White plaque with thick, folded surface	Buccal mucosa, tongue



Figure 30.1 Bohn's nodules along the upper alveolar ridge.



Figure 30.3 Eruption cysts on the lower alveolar ridge of an infant.



Figure 30.2 Epstein's pearls of the hard palate.

Ectopic thyroid tissue

Ectopic thyroid tissue is defined by the development of thyroid tissue outside the usual pretracheal position (inferior to the thyroid cartilage). This abnormality results from an arrest or irregularity in thyroid descent during embryologic development. Ectopic thyroid tissue, also referred to as a thyroglossal duct cyst, may be classified as lingual, sublingual, pretracheal, or substernal. Lingual is the most common type, representing over 90% of cases. A lingual thyroglossal duct cyst presents as a painless, nodular mass in the cervical midline or at the base of the tongue between the circumvallate papillae and the

epiglottis. Lesions may be present at birth or develop in early infancy. However, most become evident during the first or second decades of life, at which time associated symptoms may occur.^{16–19}

Thyroglossal duct cysts are a rare but serious cause of airway obstruction in newborns and infants: mortality rates of up to 43% have been reported. Although usually asymptomatic, lesions may be associated with cough, dysphagia, hemorrhage, or pain. If a cutaneous tract is present, mucous drainage can occur.

Sebaceous hyperplasia of the lip (Fordyce spots or granules)

Fordyce spots are collections of normal sebaceous glands within the oral cavity. Lesions appear as white to yellow macules and papules visible through the transparent oral mucosa. The papules measure 1–3 mm and may be clustered (Fig. 30.4). Plaques form when large numbers of sebaceous glands coalesce. Sebaceous hyperplasia is most commonly seen on the upper lip, but may also be evident on the buccal mucosa, tongue, gingiva, or palate. No treatment is warranted, as these lesions are asymptomatic, resolve spontaneously, and are of no medical consequence.⁶ Superpulsed CO₂ laser has been reported to be safe and effective in a small number of cases.²⁰



Figure 30.4 Sebaceous hyperplasia (Fordyce spots) involving the lower mucosal lip.

Nevus sebaceus

Nevus sebaceus (see [Chapter 26](#)) is a common congenital lesion that usually occurs on the scalp and face, but may be seen in continuity with growths in the oral cavity. Cutaneous lesions present as yellow, verrucous plaques ([Fig. 30.5](#)) that enlarge with the growth of the child and often become thicker in puberty. Mucosal lesions most often present as linear papillomatous plaques on the gingivae, palate, tongue and buccal mucosa. Intraoral lesions can be associated with dental anomalies and mandibular cysts.²¹ Extensive and multiple nevus sebaceus may be associated with cerebral, ocular, and skeletal abnormalities as part of sebaceous nevus syndrome.

White sponge nevus (of Cannon)

White sponge nevus is a rare, benign condition inherited as an autosomal dominant trait. Typical lesions are asymptomatic white plaques in which the oral mucosa appears thickened and folded, with a spongy texture ([Fig. 30.6](#)). The most common location for a white sponge nevus is on the buccal mucosa, often in a bilateral distribution. Extraoral locations, such as labial, nasal, vaginal, esophageal, and anal mucosa, are uncommon, and such lesions usually do not occur in the absence of oral involvement.²² The white sponge nevus is most often present at birth or discovered during early childhood.²³

The clinical differential diagnosis of white sponge nevus includes candidiasis, leukoderma, leukoplakia, lichen planus, and local irritation. White sponge nevus is sometimes seen in association with pachyonychia congenita. However, the clinical and histologic findings are usually characteristic enough to differentiate this condition from other white mucosal lesions.²⁴ The histopathology of a white sponge nevus shows epithelial thickening with hyperkeratosis and acanthosis. The suprabasal cells exhibit intracellular edema with pyknotic nuclei and compact aggregates of keratin intermediate filaments within the upper spinous layer.²⁵ White sponge nevus is a benign disorder that does not require treatment.

Granular cell tumor

The granular cell tumor, first described in 1926, was originally thought to arise from skeletal muscle and was hence named a granular cell myoblastoma.²⁶ However, more recent immunohistochemical testing suggests a neural origin.²⁷ Intraoral granular cell tumors most commonly occur on the tongue, but may also affect the lips and gingiva. The lesion is typically a solitary, small (<3 cm), firm, asymptomatic nodule, with a smooth,



Figure 30.5 Nevus sebaceus extending into oral cavity. (Courtesy of Ilona Frieden.)



Figure 30.6 White sponge nevus.

nonulcerated surface. These lesions may rarely cause obstruction of the oral cavity.²⁸

The differential diagnosis includes other benign neural neoplasms (neuromas, neurofibromas), and vascular tumors (hemangiomas, venous malformations).^{29–32} Histologically, large, eosinophilic granular cells are arranged in clusters and fascicles. Pseudoepitheliomatous hyperplasia of the overlying epithelium may be present, mimicking squamous cell carcinoma.³³

Although the majority of granular cell tumors are entirely benign, these tumors can be locally invasive and metastases have been rarely reported. Surgical excision is recommended and curative. Recurrences are uncommon.³⁴

Neurofibroma

A neurofibroma is a tumor of neural origin, which may occur as an isolated finding or in association with the syndrome of neurofibromatosis. Neurofibromatosis may be difficult to diagnose in the newborn period, when many of the features of the syndrome are not yet evident.

Neurofibromas may be found on the skin or within the oral cavity, although intraoral lesions are exceedingly rare in the newborn. The most common intraoral location is the tongue, though tumors have also been observed over the buccal mucosa and palate. Oral lesions are typically asymptomatic, slow-growing, soft nodules, of the same color as the surrounding



Figure 30.7 Black hairy tongue. (Courtesy of Erin Mathes.)

mucosa. Neurofibromas range in size from a few millimeters to a few centimeters in diameter. Histologically, the tumor is unencapsulated and composed of Schwann cells, perineural cells, and fibroblasts. Neurofibromas are benign and can be electively surgically excised with little risk of recurrence.^{35,36}

INFECTIONS

Thrush

The oral mucous membranes are the most frequent site for yeast colonization in infants. *Candida albicans* causes the white pseudomembranes (thrush) on the palate, gums, gingivae, tongue or buccal mucosa. Removal of the plaques leaves an underlying area of erythema. This is a clinical diagnosis that can be confirmed with KOH or culture. Thrush can be treated with nystatin oral suspension 200 000 units (2 mL) on the tongue four times daily for 7–10 days. Fluconazole may be more effective than oral nystatin and should be considered for treatment failures. Treatment of immunocompromised oropharyngeal candidiasis with systemic azoles can be beneficial.

Black hairy tongue (lingua pilosa nigra)

Black hairy tongue is characterized by accumulation of keratin on the filiform papillae that give the central dorsal tongue a brown-black appearance (Fig. 30.7). This condition is usually seen in adults but has been reported in an infant as young as 2 months of age.³⁷ Although the etiology is unknown, black hairy tongue is attributed to bacterial or yeast infections as well as chronic antibiotic use. Treatment involves improving oral hygiene. Brushing of the tongue with toothpaste three times a day often helps this condition.

Herpangina and hand, foot, and mouth disease (HFMD)

Herpangina and HFMD (see Chapter 13) are common illnesses caused by echoviruses, predominantly coxsackievirus A16. Herpangina is characterized by fever, sore throat, anorexia, and sometimes abdominal pain. Multiple 1–2 mm vesicles develop on the uvula, tonsils, pharynx, and soft palate. In HFMD, patients have vesicles and erosions on the buccal mucosa in addition to the oral lesions of herpangina. Patients also have oval gray-white vesicles and erythematous papules and macules on the hands, feet and buttocks.

The diagnosis of both diagnoses above is made clinically but can be confirmed with PCR.³⁸ Treatment is supportive and the course lasts less than 1 week.

Herpetic gingivostomatitis

Herpetic oral infections are usually caused by HSV-1 (see Chapter 13). There may be a prodrome of fever, vomiting, and irritability. The infant may also have tender cervical or submental lymphadenopathy. Small vesicles on an erythematous base may develop on the tongue, palate, pharynx, buccal mucosa, lips and floor of the mouth. In contrast to aphthous ulcers, the lesions coalesce into irregular shallow ulcers. Due to the pain, the infant may have difficulty with feeding.

Diagnosis can be confirmed with a Tzanck smear, viral culture, or enzyme-linked immunosorbent assay (ELISA). Treatment includes supportive care and oral acyclovir. The course usually lasts less than 2 weeks.

Human papillomavirus

Oral verrucae or papillomas occur less frequently in children and infants than other forms of HPV infection (see Chapter 13).³⁹ Exophytic, pedunculated or sessile papules with a papillated white or pink surface can present anywhere on the oral mucosa, but are most common on the tongue, palate, and labial mucosa.³⁹ When associated with laryngeal papillomas the infant or child may also have a hoarse voice or respiratory symptoms.⁴⁰ Vertical transmission of HPV during delivery, or in utero is the most likely, but horizontal transmission by household members and transmission from sexual abuse are also possible.^{39–41} If necessary, a clinical diagnosis of oral HPV infection can be confirmed by biopsy. HPV types 6, 11, 16, and 18 are most commonly found in oral papillomas. Treatment should depend on the severity of the presentation and associated symptoms. Treatment options include watchful waiting (as most spontaneously resolve within 1–2 years); destructive modalities such as cryotherapy and laser; and excision by tangential shave.³⁹

VASCULAR LESIONS (see Chapters 21 and 22)

Infantile hemangiomas (IH)

IH of the mucosa in newborns most commonly develop within the first few days to weeks of life. Most often IH involve the oral mucosa (lips, buccal mucosa, or palate), but can also involve the nasal and ocular mucosa (Fig. 30.8). Superficial lesions consist of bright red papules, nodules or plaques, whereas deeper lesions are generally flesh colored, and may have a bluish hue or overlying telangiectasias. Lesions with a combination of both superficial and deep features are also common.

Hemangiomas of the oral cavity are prone to trauma, which can lead to ulceration and/or bleeding, particularly during the newborn period. The lip can also be a high-risk location for deformity and scarring, particularly when lesions ulcerate or are superficial and cross the vermillion border. There is also a known association between hemangiomas in a cervicofacial, or ‘beard’ distribution (preauricular skin, chin, anterior neck, or lower lip) and airway hemangioma. At-risk infants should be followed closely during the newborn period for the development of stridor or other signs of airway compromise, in which case direct visualization of the airway can provide a definitive diagnosis.^{42,43} Treatment indications and options for hemangioma treatment are discussed in Chapter 21. Ulceration



Figure 30.8 Infantile hemangioma of the lower lip.

of a lip hemangioma can be particularly difficult to manage owing to the challenges of wound care in this location, and because associated pain can interfere with feeding. Such cases may require additional management with beta blockers, corticosteroids, laser, or excisional surgery.^{44,45}

Lymphatic malformations

Lymphatic malformations (LM) are benign, structural malformations of lymphatic vessels, and are much less common than hemangiomas. They are congenital, but sometimes do not manifest until later in childhood. No known sexual predilection or hereditary predisposition exists. Unlike hemangiomas, LM remain static or undergo slow expansion over time, and rarely undergo any significant degree of involution.^{46–48}

The cervicofacial region is a common site for LM. Lesions may be localized, diffuse or multiple in distribution, and may be microcystic ('lymphangioma'), macrocystic ('cystic hygroma') or combined. Microcystic lesions of the skin present as translucent papules or nodules, which often turn red or purpuric due to intralesional bleeding (Fig. 30.9). The most common location for intraoral LM is the tongue, although the lips, buccal mucosa, palate, or alveolar ridges may also be affected. LM of the tongue most commonly affects the dorsal anterior two-thirds and may result in macroglossia and difficulties with feeding and speech.^{47–49} Large macrocystic (Fig. 30.10) or combined LM of the posterior triangle of the neck, which often present as fluctuant, flesh-colored tumors, may also involve the floor or the mouth and submandibular space. Bacterial cellulitis occurring within cervicofacial LM is potentially dangerous because of the risks of airway compromise. In such instances, systemic antibiotics should be administered at the first sign of swelling, pain, redness, or systemic toxicity.

Histologically, LM consist of multiple lymphatic channels lined by single or multiple layers of endothelial cells. Treatment is rarely necessary in the first year of life, and is generally reserved for lesions causing functional compromise or cosmetic deformity. MRI is the best means of determining lesion extent and microcystic or macrocystic morphology, which is generally necessary before decisions regarding treatment can be made.

The mainstay of therapy for LM includes surgery and/or sclerotherapy, though cure is rarely achieved except for the smallest, most well-localized lesion. Attempts at surgical resection are often accompanied by a variety of intraoperative



Figure 30.9 Microcystic lymphatic malformation (lymphangioma) of the tongue. (Courtesy of Ilona Frieden.)



Figure 30.10 Large, oral lymphatic malformation (cystic hygroma).

and postoperative complications, including recurrence. Sclerotherapy with agents such as absolute ethanol, sodium tetradecyl sulfate, or doxycycline, can be used for treatment of macrocystic LM, alone or in conjunction with surgical techniques.^{50,51} Microcystic LM of the tongue can also be treated with laser photocoagulation, though this is also a temporary measure.^{52,53}

Venous malformations

Venous malformations (VM) are slow-flow structural anomalies of the venous vasculature, which are generally present at birth but may not manifest until later in childhood. Lesions most commonly involve the face and oropharynx, but may occur in any anatomic location. Though usually solitary, lesions may be multiple, especially when associated with the autosomal dominant, familial cutaneous–mucosal VM syndrome, or blue rubber bleb nevus syndrome, both characterized by small dome-shaped lesions. VMs are bluish, compressible nodules, which slowly refill upon release and are often intermittently painful. Lesions may result in skeletal alterations, such as facial asymmetry, dental malalignment, open mouth deformity, and bony hypertrophy.

MRI with or without venography or Doppler ultrasound is the best way to confirm the diagnosis of a venous malformation and determine the extent of tissue involvement. In addition, the

presence of phleboliths is highly characteristic of the diagnosis. Extensive lesions may be complicated by a localized, intravascular coagulopathy, characterized by a normal or moderately low platelet count and fibrinogen, increased D-dimers, and normal prothrombin and partial thromboplastin times.

VMs characteristically undergo slow expansion over time. Treatment is rarely necessary in the first years of life, and is generally reserved for lesions leading to functional compromise, bleeding, coagulopathy, or cosmetic disfigurement. Depending on the location and size of the lesion, surgical excision and/or sclerotherapy can be considered.⁵⁴

Port-wine stain

A port-wine stain (PWS) is a common capillary malformation in newborns. Histopathology shows a normal number of dilated capillaries in the superficial dermis. The well-demarcated vascular stains grow in proportion to the growth of the child.

An orodental PWS may lead to hyperplasia of the gingivae, oral bleeding, overgrowth of bony structures, and possible interruption in dental eruption. This is thought to be from increased blood flow to the areas.⁵⁵

Pyogenic granuloma

Pyogenic granuloma is an acquired vascular lesion that most commonly presents on the skin, but is not uncommonly seen on the mucous membranes. The typical clinical presentation is a solitary red papule with a collarette of scale at the base that occurs in areas prone to trauma and may bleed. Treatment includes shave excision with electrodesiccation of the base, which helps prevent recurrence. Pulsed-dye laser has been used in smaller lesions.⁵⁶

SIGNS OF EXTRACUTANEOUS DISEASE

Macroglossia

Macroglossia is defined as a resting tongue that protrudes beyond the teeth or gum line (Figs 30.11, 30.12). When this



Figure 30.11 Macroglossia in an infant with Beckwith-Wiedemann syndrome.

is present in a newborn, a thorough evaluation should be performed to rule out genetic, metabolic, or other possibly contributing factors. True macroglossia may be 'primary,' whereby the tongue is enlarged due to hyperplasia or hypertrophy of normal lingual structures, or, more commonly, 'secondary' to an underlying process, as with a lymphangioma or in amyloidosis (Box 30.1).

True macroglossia must be distinguished from pseudomacroglossia. In pseudomacroglossia, the tongue is normal size but functionally enlarged as a result of a small or inferiorly displaced mandible. This situation occurs in the Pierre-Robin syndrome, and is also seen in some newborns ultimately diagnosed with cerebral palsy. An enlarged tongue may affect feeding, speech, and respiration. In later infancy, macroglossia may also cause malocclusion as a result of increased pressure on the teeth.



Figure 30.12 Protruding tongue from macroglossia.

BOX 30.1 PRIMARY AND SECONDARY CAUSES OF MACROGLOSSIA

PRIMARY

- Muscular hypertrophy

SECONDARY

Congenital

- Lymphangioma
- Hemangioma
- Vascular malformations
- Beckwith-Wiedemann syndrome
- Trisomy 4p syndrome
- Triploidy syndrome
- Trisomy 21 syndrome (Down syndrome)
- Fetal face syndrome (Robinow syndrome)

Metabolic storage disease

- Mucopolysaccharidoses II, III, IV
- Generalized gangliosidosis S
- Glycogen storage disease
- Endocrine disorders
- Congenital hypothyroidism

Tumors

- Granular cell tumor
- Neurofibroma

Surgical trimming or reduction of the tongue is often effective in reducing tissue bulk. Between 4 and 7 years of age is the optimal time for surgical correction if immediate intervention is not mandated by airway obstruction.⁵⁷ However, therapeutic intervention, when feasible, should be aimed at treating any underlying cause.⁶

Natal teeth

Natal teeth are defined as teeth present at birth and must be differentiated from neonatal teeth, which erupt during the first month of life. The reported incidence of both natal and neonatal teeth varies widely, but is decidedly rare. Both may occur in either premature or term infants. However, natal teeth occur three times more often than neonatal teeth and are twice as common in females. Two-thirds of natal teeth occur in pairs. The most common location for natal teeth is at the sites of the central mandibular incisors (85%), followed by the maxillary incisors (11%) (Fig. 30.13).^{58–60} Estimates suggest that only 1–10% of natal teeth are supernumerary.⁶¹

Although the exact etiology for natal teeth remains unknown, it appears that the primary tooth bud develops in a more superficial location than normal, and therefore erupts prematurely.⁶²

Many syndromes have been associated with natal teeth (Table 30.2), and newborns with this finding should be examined carefully. Reported associations include congenital syphilis, endocrine disturbances, febrile systemic illness, hypovitaminosis, and pyelitis during pregnancy.⁸

Natal teeth usually represent deciduous rather than supernumerary teeth, which can be distinguished by radiography. Supernumerary teeth are extraneous teeth, which should be extracted as they may interfere with normal tooth eruption. The lower central incisors are normally the first teeth in the oral

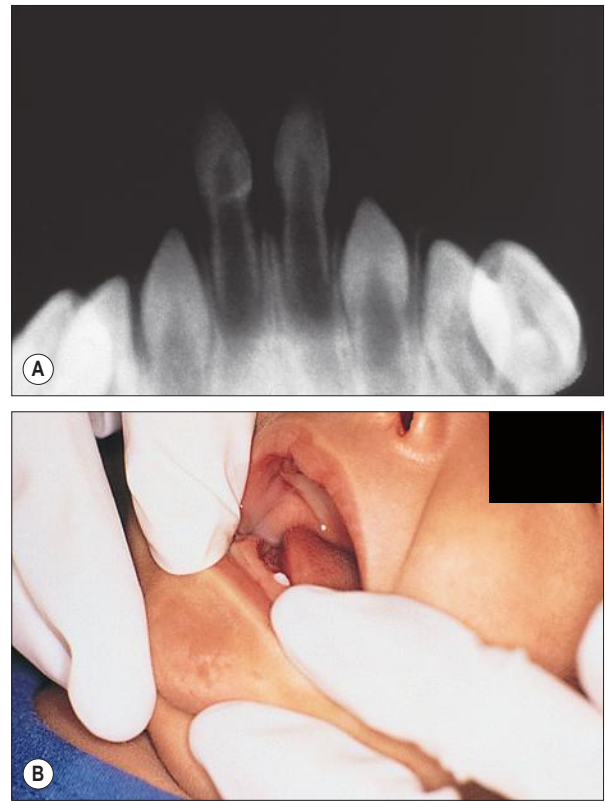


Figure 30.13 (A) Radiograph of natal teeth. (B) Natal teeth on the lower alveolar ridge of an infant.

TABLE 30.2

Syndromes associated with natal teeth

Syndrome	Associated anomalies	Inheritance/chromosomal abnormality/prevalence
Ellis-van Creveld (chondroectodermal dysplasia)	Bilateral postaxial polydactyly of hands, chondrodysplasia of long bones resulting in acromesomelic dwarfism, ectodermal dysplasia affecting nails/teeth, congenital heart malformation	Autosomal recessive Not known 7/1 × 10 ⁶
Hallermann–Streiff	Dyscephaly, hypotrichosis, micro-ophthalmia, cataracts, beaked nose, micrognathia, proportionate short stature	Sporadic Not known 150 cases to date
Pachyonychia congenital (type 1: Jadassohn–Lewandowsky or type 2: Jackson–Lawler)	Dystrophic nails, palmoplantar keratosis, hyperhidrosis, follicular keratosis, oral leukokeratosis, cutaneous cysts	Autosomal dominant Keratin mutation (type 1: 6a/16; type 2: 6b/17) 0.07/1 × 10 ⁶ 9:5 male to female ratio
Pallister–Hall (hypothalamic hamartoblastoma)	Hypothalamic hamartoblastoma, craniofacial abnormalities, postaxial polydactyly, cardiac and renal defects	Sporadic Not known 13 cases to date 8:5 male to female ratio
Wiedemann–Rautenstrauch	Endocrine dysfunction, aged facies, frontal and biparietal bossing, small facial bones, sparse scalp hair, prominent scalp veins, small beaked nose, low-set ears	Autosomal recessive Not known 1 case to date
Natal teeth, patent ductus arteriosus, intestinal pseudo-obstruction	Dilatation/hypermobility of small bowel, short or microcolon without obstruction, incomplete rotation of midgut, patent ductus arteriosus	X-linked recessive Not known 2 cases to date, brothers

(Reproduced with permission from Hebert AA. Mucous membrane disorders. In: Schachner LA, Hansen RC, eds. *Pediatric dermatology*, Volume 1, 4th edition. Philadelphia: Mosby, 2011.)

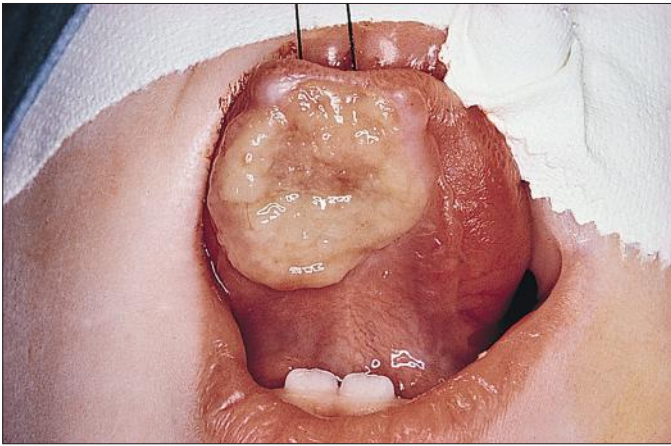


Figure 30.14 Traumatic ulcerative granuloma lesion of the tongue in Riga–Fede syndrome.

cavity to erupt. The condition of Riga–Fede describes a traumatic ulcerative lesion of the tongue or frenulum, produced when an infant rakes the tongue over the primary lower incisors, which may be mobile and/or have poorly formed crowns (Fig. 30.14). This condition may be related to pain insensitivity, and has been associated with familial dysautonomia,^{8,63} although Riga–Fede can be seen in normal newborns. This oral ulcerative condition has also been associated with congenital autonomic dysfunction, microcephaly, Lesch–Nyhan syndrome and Tourette syndrome.⁶⁴

Treatment of natal teeth is dependent on morphology, the amount of root development, and mobility. A pediatric dentist should be involved in the care plan. Two cases were managed by covering the incisal margin with photopolymerizable resin which facilitated the healing of the ulcerations.⁵⁹ If the tooth is only minimally loose, it will tend to stabilize over time and can be left in place. Problematic teeth should be extracted to prevent trauma or aspiration.^{65,66} In the setting of a tongue ulceration of Riga–Fede disease, prompt diagnosis and management is essential to avoid deformity or mutilation of the tongue, dehydration and poor growth.⁶⁷ In all newborns, the administration of prophylactic vitamin K (0.5–1.0 mg IM) is recommended before tooth extraction due to the potential risk of hemorrhage.⁶⁸

Congenital fistulae of the lower lip

Congenital fistulae of the lower lip (or lip pits) are rare developmental anomalies. The estimated frequency of lower lip pits in Caucasians is uncommon, with approximately 1 in 100 000 persons affected; the frequency in the black population is rare. Clinically, bilateral indentations are seen on the vermilion portion of the lower lip. The pits are usually 1 cm apart and equidistant from the midline. The defect results from incomplete closure of the furrows on the fetal mandibular process. The pits range in depth from a few millimeters to 25 mm; longer fistulae can traverse the orbicularis oris muscle. The proximal opening of the fistula at the lip may extrude saliva, either spontaneously or during mastication. Histologically, the fistula lumen is lined by stratified squamous epithelium, similar to lip mucosa. At the distal end of the fistula, scattered acini of mucinous glands with tubular ducts are present. True salivary glands are not seen.^{6,69}

Congenital fistulae are inherited as an autosomal dominant trait with an estimated penetrance of 80–100%. The presence



Figure 30.15 Lobulated tongue of a female infant with orofacial-digital I syndrome.

of a single fistula is considered an incomplete expression of the trait and not a separate entity. Less severe forms may occur and present as simple elevations of a portion of the vermilion border or as an isolated ptosis of the lower lip.⁷⁰ The evaluation of a patient with lower lip pits should include a search for other possible anomalies. Lip pits are strongly associated with the formation of cleft lip and/or palate. This association approaches 80% and is now referred to as the Van de Woude syndrome. Nearly all cases of Van de Woude syndrome have shown linkage to a region at chromosome 1q32–p41 or 1p34. This autosomal dominantly inherited clefting syndrome shows high penetrance but variable expressivity.⁷¹ Newborn infants with single lip pits are at equal risk with those having double pits for associated clefting. Congenital fistulae of the lip are only treated to correct visible deformity or to eradicate significant aberrant salivation.^{6,69,70,72–74}

The best time for surgical repair of the lower lip may be between 10 and 12 months of age. Surgical intervention at this time also helps with parental concerns to normalize the appearance of their child.⁷⁴

Orofacial-digital syndrome, type I

Orofacial-digital (OFD) syndrome is a rare and complex condition. Nine types are currently recognized.⁷⁵ Oral abnormalities are the most consistent and characteristic findings of type I OFD (also known as Papillon–Léage–Psaume syndrome). Features may include multiple hyperplastic frenula between the buccal mucosa and alveolar ridge, cleft lip (45%) or palate (80%), a lobated or bifid tongue (30–40%) with small hamartomas (70%) (Fig. 30.15), dental caries, and/or anomalous anterior teeth. Distinguishing facial features are frontal bossing, hypoplasia of the malar bones and alar cartilages, a broad nasal root, and milia of the ears. Skeletal findings include asymmetric shortening of digits, clinodactyly and brachydactyly of the hands (45%), and unilateral polydactyly (25%) of the feet. Infants may also have a dry, rough scalp with significant alopecia.

This form of OFD is part of a heterogeneous group of PFD syndromes.⁷⁶ The *OFDI* gene is named *Cxof5* (Xp22.2–22.3). The condition is seen in one in 50 000 live births.

Newborns with OFD type I may also have internal manifestations, the most common of which are multiple renal, hepatic, or pancreatic cysts. OFD I is considered a distinct subset of this syndrome because of the X-linked dominant inheritance pattern and this association with polycystic kidney disease.⁷⁶

Significant CNS abnormalities, especially agenesis or absence of the corpus callosum, also occur. The overall prognosis is poor: one-third of affected patients die within the first year of life. Therapy must be individualized based on the presence of visceral anomalies. Surgical intervention may be necessary to ensure proper feeding and oral communication.^{6,77,78}

Oral and genital ulcerations with immunodeficiency

The presentation of oral and genital ulcers in a newborn may be a sign of underlying congenital immunodeficiency. In particular, ulcers in these locations appear to be a distinctive marker and are often the presenting feature of severe combined immunodeficiency disease with T- and B-cell lymphopenia (T-B-SCID) in Athabascan-speaking Native American infants.⁷⁹ In this population, ulcers are typically punched-out and deep, albeit without invasion to underlying structures, and do not result in functional sequelae or significant scarring. This is to be distinguished from the condition noma neonatorum, which is a rare condition of preterm infants in developing countries. Noma neonatorum causes aggressive orofacial tissue gangrene, accompanied by a high mortality rate, and is most commonly associated with *Pseudomonas aeruginosa* sepsis.^{80,81} In contrast, the ulcers found in Native American children with T-B-SCID are most likely a result of T-cell immunodeficiency combined with a genetic predisposition. In such children, treatment of the underlying condition with bone marrow transplantation results in resolution of the ulcers. Early recognition and diagnosis can lead to prompt intervention and prevention of complications.⁷⁹

Behçet disease

Behçet disease is a complex, multisystem disease characterized clinically by the presence of oral aphthae and at least two of the following: genital aphthae, synovitis, cutaneous pustular vasculitis, posterior uveitis, or meningoencephalitis. The most common features of neonatal Behçet disease are oral ulcerations, skin lesions, fever and leukocytosis but only half of the patients described would fulfill the classic diagnostic criteria (based on an adult patient series). In addition, a treatment consensus for neonatal Behçet disease has yet to be published.⁸² Neonatal cases have been described in which affected mothers had oral and genital ulcerations during pregnancy.^{83,84} A case of transient neonatal Behçet disease with life-threatening complications has been reported.⁸⁵

Although uncommon, pediatric Behçet disease does occur. In comparison with adults, oral and genital ulcers are less common in children with Behçet disease. Uveitis, however, is more common. As in adults, ocular lesions in children pose a serious threat because they may lead to blindness.⁸⁶

Acatalasemia

Acatalasemia is a genetically heterogeneous disease characterized by an inherited absence of the enzyme catalase. Affected infants are unable to degrade endogenous or exogenous hydrogen peroxide, which accumulates, resulting in oxidation deprivation. The soft tissues of the mouth and nasal mucosa are preferentially affected, leading to ulceration, necrosis, and in severe cases gangrene. The physical examination is otherwise normal. The diagnosis is confirmed by the absence of blood catalase. Therapy consists of meticulous oral hygiene, early removal of diseased teeth and tonsils, and the administration of systemic antibiotics as necessary to control bacterial proliferation.^{6,87}

PIGMENTARY DISORDERS

Lingual melanotic macule

Congenital lingual melanotic macules have been observed as solitary or multiple, well-circumscribed, brown lesions on the dorsal surface of the tongue at birth that grow proportionately to the tongue (Fig. 30.16). Histological features are those of increased basal pigmentation with minimal melanocytic hyperplasia and mild pigment incontinence. It is distinct from macular pigmentation, and appears to be a benign process. The diagnosis of congenital lingual melanotic macule should be considered if the pigmented macules are present at birth and grow proportionately with the child.⁸⁸

Macular pigmentation

Macular pigmentation of the oral mucosa is a normal variant found in darker-skinned persons. Several patterns of pigmentation may occur. Most commonly, a pigmented band is present at the junction of the free and attached alveolar mucosa. Patchy pigmentation may also be evident over the buccal mucosa, on the lips, and on the floor of the mouth (Fig. 30.17). When the tongue is involved, which is rare, the pigment is localized to the filiform papillae. The increased pigmentation occurs as a result of an increase in melanocytic activity rather than an increase in the number of melanocytes. No therapy is necessary.⁸⁹



Figure 30.16 Lingual melanotic macule on the dorsal tongue surface.



Figure 30.17 Macular hyperpigmentation involving the lower lip.



Figure 30.18 Sucking callus of the upper lip.

MISCELLANEOUS LESIONS

Annulus migrans (geographic tongue)

Annulus migrans is a common condition that may present as early as 2 weeks of life. Another name for this condition is benign migratory glossitis. Characteristically, erythematous patches are due to depapillation. The lesions are often migratory and transient in nature. The etiology of annulus migrans is most likely reactive in nature; reported associated disorders have included psoriasis (especially pustular), Reiter syndrome, atopic and seborrheic dermatitis, and spasmodic bronchitis of childhood. Histologically, geographic tongue is indistinguishable from pustular psoriasis or Reiter syndrome. Therapy of this benign condition is generally unsuccessful and unwarranted.^{6,90}

Sucking calluses

Sucking calluses (or sucking pads) develop on the lips or buccal mucosa as solitary, oval thickenings (Fig. 30.18). When these lesions are congenital, they are indicative of vigorous sucking in utero. Presentation after birth is more common in breastfed black infants.⁹¹ Histology reveals a thickened epidermis secondary to intracellular edema and hyperkeratosis. Sucking calluses involute spontaneously within a few days or weeks after birth, or on cessation of breastfeeding.^{6,14}

Bednar's aphthae

Bednar's aphthae are ulcers located on the posterior palate that are thought to be from trauma. They are large and tend to coalesce. Pacifiers and vigorous sucking may be responsible. The differential diagnosis includes herpangina and herpetic stomatitis. Treatment of the lesions includes minimizing trauma.

Disorders of the genital mucous membranes

LABIAL ADHESIONS

Labial adhesions⁹² are exceedingly rare during the newborn period. The rarity of this finding has been attributed to the presence of maternal estrogens at birth. Infants between the ages of 13 and 23 months are most commonly affected, with an incidence of 3.3%. Clinically, a thin membrane extends between the labia, which may partially or completely conceal the vaginal opening. Recommended treatments include A+D Ointment®



Figure 30.19 Perianal pyramidal protrusion in a female infant.

for asymptomatic cases, and topical estrogen cream or ointment if urinary or vaginal drainage is impaired.^{93,94} Use of potent topical steroids have been reported in prepubertal patients but few references to the neonatal period are available.⁹²

PERIANAL PYRAMIDAL PROTRUSION

Perianal pyramidal protrusion (see Chapter 17) is an increasingly recognized entity characteristically located on the perineal median raphe, anterior to the anus. Clinically the lesion is pyramidal in shape, with a smooth, red, or rose-colored surface (Fig. 30.19). The average age at presentation is 14.1 months, and 94% occur in females. Histologic examination shows epidermal acanthosis, marked edema in the upper dermis, and a mild dermal inflammatory infiltrate.⁹⁵ The pathogenesis is unknown, but some cases have been related to constipation and lichen sclerosus et atrophicus.^{96,97} This condition is not associated with child abuse. Differential diagnosis includes genital warts, granulomatous lesions of inflammatory bowel disease, rectal prolapse, hemorrhoids, acrochordons, and perineal midline malformation. Although most lesions show spontaneous reduction without any specific treatment, treating associated constipation may hasten resolution.^{95,98,99}

PERINEAL GROOVE

A moist sulcus extending from the posterior fourchette to the anterior edge of the anus is called a perineal groove (Fig. 30.20). Theories as to why this rare congenital malformation occurs include distorted fusion of the medial genital folds in the central area between the perineal raphe and the vestibule or as a function of an open cloacal duct.^{100–103} In those young girls with the perineal groove who tend to develop recurrent infections, treatment with surgical excision of the groove is recommended.¹⁰²

HYMENAL TAG

Hymenal tags are fleshy protrusions that extend from the hymen. These have been defined as a 'flap' or 'appendage' extending ≥ 1 mm from the hymenal rim.¹⁰⁴ Tags develop more often superiorly and inferiorly on the hymen (rather than on



Figure 30.20 Perineal groove in female infant. (Courtesy of Moise L. Levy.)

the lateral portion) due to their origin from the septa.¹⁰⁵ Hymenal tissue may be observed to be redundant in neonates and a portion of the hymen may appear translucent.¹⁰⁶ Tags may be present and noted at the time of birth or may develop during early childhood. No therapy is warranted.

URETHRAL RETENTION CYST

The urethral retention cyst is an inclusion cyst that forms at the urethral opening in newborn boys. This lesion is simply a milium, which develops either as a result of friction or from remnants of epithelial tissue trapped along a line of skin fusion. No therapy is necessary, as the white, firm, smooth-surfaced papule will rupture spontaneously and be shed during the first weeks of life. These cysts are not likely to cause urinary retention or symptoms.¹⁰⁷

ADHESIONS AFTER CIRCUMCISION

The estimated rate of newborn circumcision in the USA is approximately 65% of all male offspring. While the vast majority of circumcisions are without postoperative complications, re-evaluations of the surgical site represented 7.4% of pediatric urology visits in one outpatient clinic.¹⁰⁸ The most common finding that resulted in revision circumcision was the presence of excess foreskin resulting in an uncircumcised appearance and a poor cosmetic outcome. Other complications can include: preputial adhesions, meatal stenosis skin bridges, aborted circumcisions due to hypospadias, recurrent phimosis, paraphimosis, iatrogenic buried penis, penile rotation, and wound dehiscence. Examples of late complications are seen in [Figure 30.21](#). The majority of such surgical complications are said to be avoidable by the use of meticulous circumcision technique and careful postoperative wound care.¹⁰⁸



Figure 30.22 Lichen sclerosis in a male. (Reproduced with permission from Becker K. Lichen sclerosis in boys. *Dtsch Arztebl Int* 2011; 108(4):53–8.)

The etiology of penile adhesions after circumcision is unknown but these may result from incomplete lysis of the physiological adhesions at circumcision.¹⁰⁹ Following circumcision, two moist surfaces touch each other and that phenomenon may lead to the formation of adhesions that are circumferential or single synechial bands. The majority of these bands will resolve without intervention over time. The longer the time period between the circumcision, the less likely it is that adhesions will form.¹⁰⁹

LICHEN SCLEROSIS

Lichen sclerosis (see [Chapter 17](#)) is rare in the neonate but may develop in infancy and most often affects females. The classic morphology in females is white, glistening atrophic plaques on the vulvar and perineal skin with occasional telangiectasias and fine wrinkling of the skin. Pruritus, constipation, dysuria and pain are common associated symptoms. Progressive anatomic distortion may occur if lichen sclerosis is left untreated. High potency topical steroids are the treatment of choice, but the disease may recur after treatment is stopped.

The characteristic findings in males are sclerotic white porcelain-like alterations at the distal portion of the prepuce ([Fig. 30.22](#)). These changes, which may present as a whitish ring on the distal penis, can cause progressive phimosis. Cicatricial phimosis should prompt an evaluation for lichen sclerosis. The ultimate degree of involvement of the meatus and urethra depends on the disease severity and the duration of the sclerosis before adequate intervention occurs. Lichen sclerosis is seen more often in males with hypospadias. Ultimately 10–40% of all surgically treated phimosis cases are due to lichen sclerosis. In males, the name balanitis xerotica obliterans refers to the prepubertal form of lichen sclerosis.¹¹⁰ Treatment is with topical steroids if the disease is mild, but surgery with total circumcision yields the most definitive clinical cure. The resected foreskin should be examined histologically to confirm the diagnosis.

PYODERMA GANGRENOSUM

Pyoderma gangrenosum (PG) is an ulcerative skin disorder most commonly seen on the lower legs of adults. In adults, it is

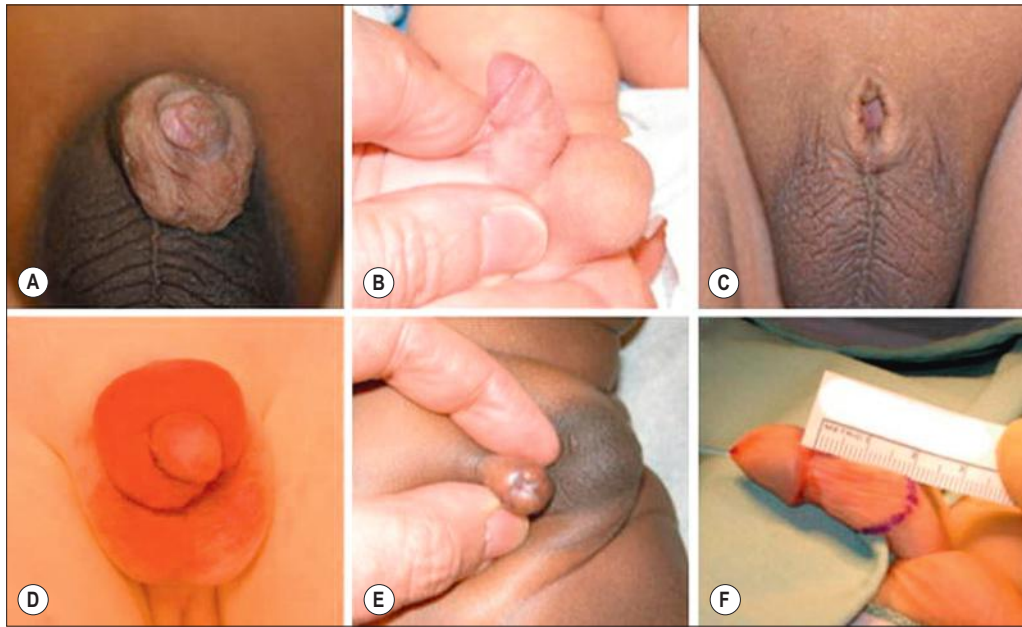


Figure 30.21 Late circumcision complications. (A) Redundant foreskin with unsightly appearance, (B) dorsal curvature, (C) buried penis, (D) paraphimosis, (E) recurrent phimosis, (F) redundant inner foreskin. (Reproduced with permission from Pieretti RV, Goldstein AM, Pieretti-Vanmarcke R. Late complications of newborn circumcision: a common and avoidable problem. *Pediatr Surg Int* 2012; 26:515–518.)

often associated with an underlying systemic disease, especially ulcerative colitis, Crohn disease, or leukemia. The condition is rare in children (4% of cases), and rarer still in infants less than 2 years of age. Diagnosis in infancy is challenging because of the atypical location of lesions (perianal or genital) and the lack of associated systemic illness. Differential diagnosis in infancy includes ecthyma gangrenosum caused by *Pseudomonas* infection, herpes simplex infection, and severe diaper dermatitis. Successful treatment has been reported with systemic, topical, and intralesional corticosteroids.¹¹¹

Disorders of the ocular mucous membranes

CONGENITAL OBSTRUCTION OF THE NASOLACRIMAL DUCT

Congenital obstruction of the nasolacrimal duct is the most common abnormality of the lacrimal system in children. Up to 6% of newborn infants are affected. Symptoms typically begin shortly after birth and are variable. Many infants will have only a wet-looking eye or overflow tearing, but most will have recurrent infections manifested by reflux or mucopurulent material from the lacrimal sac. The majority of nasolacrimal duct obstructions clear spontaneously. Simple medical management with antibiotics and massage may hasten resolution. When spontaneous resolution does not occur, ophthalmologic probing and/or irrigation may be required.^{112,113}

MUCOCELE OF THE LACRIMAL SAC

The mucocele of the lacrimal sac is a rare anomaly. It presents at birth or shortly thereafter as a bluish, cystic swelling located just below the medial canthus. The lesion is typically about 1 cm in diameter and may be confused with a hemangioma because of its color. Blockage of both the proximal and distal ends of the lacrimal drainage system leads to the accumulation of mucus within the lacrimal sac. The natural course is variable. In some cases the blockage may open spontaneously, but many lesions become infected and/or inflamed with erythema, edema, and surrounding cellulitis. Treatment includes gentle application of warm compresses and systemic antibiotics if infection is suspected. Mucoceles unresponsive to conservative treatment may require ophthalmologic probing.¹¹²

BLEPHARITIS AND CHALAZION

Seborrheic blepharitis is an inflammatory condition of the eyelid margin. In infants, seborrheic blepharitis usually occurs in association with dermatitis of the scalp (termed cradle cap) or diaper area, and is most commonly seen between the second and 10th weeks of life. The lid margins are typically erythematous and scaly, with accumulation of debris at the base of the lashes. The severity of the blepharitis usually correlates with degree of dermatitis and rarely may cause a superficial, marginal keratitis.

Treatment of seborrheic blepharitis consists of warm water compresses and gentle cleansing using a dilute amount of an isotonic (baby) shampoo. If necessary, a soft-bristled toothbrush can be used to mechanically remove the scale. A low-potency, non-fluorinated corticosteroid (hydrocortisone) or sulfacetamide ointment may then be gently massaged into the

lid margin. These procedures should be repeated daily until the blepharitis has subsided.¹¹⁴

A chalazion is caused by inflammation of a meibomian gland of the upper or lower eyelid. It presents with an erythematous, tender nodule on the lid margin. Most chalazia resolve without treatment, but patients may benefit from warm compresses, and lid hygiene (as described above). Oral azithromycin or erythromycin should be considered if there are corneal changes. If severe and persistent, patients should be referred for excision.

Blepharitis, conjunctivitis, or a chalazion may also be seen in association with periorificial dermatitis, a form of acne rosacea. Patients develop erythematous papules or pustules in the perioral, nasolabial, and periocular locations. Additional ocular findings include hyperemia, photophobia, episcleritis, keratoconjunctivitis and rarely corneal ulcers.¹¹⁵ The etiology of periorificial dermatitis is unknown but may be precipitated or prolonged by the use of topical or inhaled steroids.¹¹⁶ Periorificial dermatitis is self-limited but may take months to resolve. Patients should be screened for ocular symptoms and referred for ophthalmologic evaluation if ocular symptoms are severe. Treatment includes topical or oral antibiotics such as erythromycin, azithromycin, or metronidazole (see [Chapter 25](#)).

MOLLUSCUM CONJUNCTIVITIS

Molluscum contagiosum can present on the lid or lid margin in infants and young children. In most cases the lesions are small and umbilicated, but lesions can occasionally be multiple and >1 cm. Keratoconjunctivitis may be present and may lead to corneal complications.¹¹⁷ If asymptomatic, no treatment is necessary. However, if ocular symptoms are present, patients should be referred to ophthalmology.

COLOBOMATA

The term coloboma describes a defect such as a notch, gap, fissure, or hole caused by the loss of ocular tissue or an ocular structure ([Fig. 30.23](#)). Colobomata may occur as an isolated anomaly, but are most frequently associated with chromosomal defects, especially trisomies 13 and 18, often in association with significant central nervous system abnormalities.¹¹⁸ Infants with



Figure 30.23 Eyelid coloboma is evident, as well as a hair follicle hamartoma.

the CHARGE syndrome (congenital heart disease, choanal atresia, growth and/or mental retardation, genital hypoplasia, ear anomalies and/or deafness) have a 79% incidence of colobomata.^{119,120} Colobomata may occasionally be associated with an impaired vision. Retinal colobomas are also a regular feature of the CHIME syndrome (see [Chapter 19](#)).

GLAUCOMA

In infants, the principal signs of glaucoma are tearing, conjunctival hyperemia, photophobia, blepharospasm, corneal clouding, and an enlargement of the cornea and globe, referred to as buphthalmos ([Fig. 30.24](#)). Glaucoma in infants is usually due to a developmental disorder in which residual mesodermal tissue impedes the drainage of aqueous humor from the anterior chamber. This primary or simple congenital glaucoma is probably a multifactorial, recessively inherited condition. Other major causes of glaucoma in children are trauma, intraocular hemorrhage, ocular inflammatory disease, and intraocular tumors. Infantile glaucoma has been associated with a variety of other ocular conditions as well as a number of systemic disorders. Those systemic disorders relevant to the dermatologist include Sturge–Weber syndrome, neurofibromatosis,

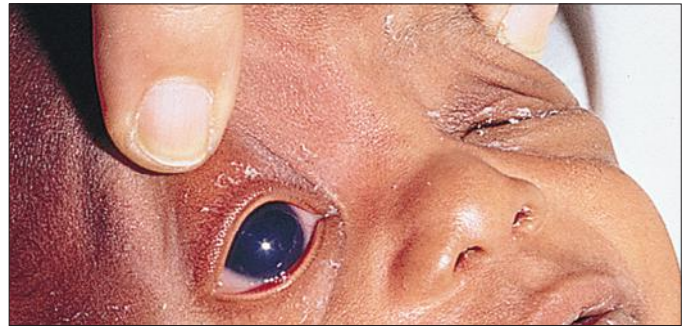


Figure 30.24 Corneal clouding characteristic of congenital glaucoma.

the congenital infection (TORCH) syndromes, and juvenile xanthogranulomas.

Access the full reference list at [ExpertConsult.com](https://www.expertconsult.com) 

Figure 21 is available online at [ExpertConsult.com](https://www.expertconsult.com) 

KEY REFERENCES

1. Rioboo-Crespo MdDel R, Planells-del Pozo P, Rioboo-Garcia R. Epidemiology of the most common oral mucosal diseases in children. *Med Oral Patol Oral Cir Bucal* 2005;10:376–87.
2. Majorana A, Bardellini E, Flocchini P, et al. Oral mucosal lesions in children from 0 to 12 years old: ten years' experience. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;110:e13–18.
5. Kula KS, Josell SD. Oral problems. In: McMillan JA, Feigin RD, DeAngelis CD, et al, editors. *Oski's pediatrics: principles and practice*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 781–800.
35. Chrysomali E, Papanicolaou SI, Dekker NP, et al. Benign neural tumors of the oral cavity. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;84:381–90.
43. O TM, Alexander RE, Lando T, et al. Segmental hemangiomas of the upper airway. *Laryngoscope* 2009;119(11):2242–7.
44. Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008;358(24):2649–51.
45. Kwon EK, Seefeldt M, Drolet BA. Infantile hemangiomas: an update. *Am J Clin Dermatol* 2013;14(2):111–23.
91. Yilmaz, AE, Gorpelioglu C, Sarifakioglu E, et al. Prevalence of oral mucosal lesions from birth to two years. *Niger J Clin Pract* 2011;14(3):349–53.
102. Esposito C, Giurin I, Salvanelli A, et al. Current trends in the management of pediatric patients with perineal groove. *J Pediatr Adolesc Gynecol* 2011;24:263–5.
108. Pieretti RV, Goldstein AM, Pieretti-Vanmarcke R. Late complications of newborn circumcision: a common and avoidable problem. *Pediatr Surg Int* 2012;26:515–18.
109. Ponsky, LE, Ross JH, Knipper N, et al. Penile adhesions after neonatal circumcision. *J Urol* 2000;164:495–6.

REFERENCES

- Rioboo-Crespo MdDel R, Planells-del Pozo P, Rioboo-Garcia R. Epidemiology of the most common oral mucosal diseases in children. *Med Oral Patol Oral Cir Bucal* 2005;10:376–87.
- Majorana A, Bardellini E, Flocchini P, et al. Oral mucosal lesions in children from 0 to 12 years old: ten years' experience. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010;110:e13–18.
- Cambiaghi S, Gelmetti C. Therapy for Bohn's nodules is unnecessary, since spontaneous involution or shedding is the rule. *Int J Dermatol* 2005;44:753–4.
- Paller AS, Mancini A. *Hurwitz clinical pediatric dermatology*. 4th ed. Philadelphia: Elsevier Saunders; 2011. p. 15.
- Kula KS, Josell SD. Oral problems. In: McMillan JA, Feigin RD, DeAngelis CD, et al, editors. *Oski's pediatrics: principles and practice*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 781–800.
- Hebert AA. Mucous membrane disorders. In: Schachner LA, Hansen RC, editors. *Pediatric dermatology*, vol. 1. 4th ed. Philadelphia: Mosby; 2011. p. 644–99.
- Olson JL, Marcus JR, Zuker RM. Congenital epulis. *J Craniofac Surg* 2005;16:161–4.
- Dilley DC, Siegel MA, Budnick S. Diagnosing and treating common oral pathologies. *Pediatr Clin North Am* 1991;38:1227–64.
- Zuker RM, Buenechea R. Congenital epulis: Review of the literature and case report. *J Oral Maxillofac Surg* 1993;51:1040–3.
- Al-Qattan MM, Clarke HM. Congenital epulis: evidence against the intrauterine estrogen stimulus theory. *Ann Plast Surg* 1994;33:320–1.
- Raissaki, MT, Segkos N, Prokopakis, EP, et al. Congenital granular cell tumor (epulis). *J Comput Assist Tomogr* 2005;29:520–3.
- Steelman R, Weisse M, Ramadan H. Congenital ranula. *Clin Pediatr* 1998;37:205–6.
- Yuca K, Bayram I, Cankaya H, et al. Pediatric intraoral ranulas: an analysis of nine cases. *Yohoku J Exp Med* 2005;205:151–5.
- Weston WL, editor. Neonatal dermatology. In: *Color textbook of pediatric dermatology*. St Louis: Mosby; 1991. p. 224, 227.
- Peters R, Schock RK. Oral cysts in newborn infants. *Oral Surg* 1971;7:10–14.
- Damiano A, Glickman AB, Rubin JS, et al. Ectopic thyroid tissue presenting as a midline neck mass. *Int J Pediatr Otorhinolaryngol* 1996;34:141–8.
- Krishnamurthy GT, Bajd WH. Lingual thyroid associated with Zenker's and vallecular diverticula: report of a case and review of the literature. *Arch Otolaryngol* 1972;96:171–5.
- Leung AK, Wong AL, Robson WL. Ectopic thyroid gland simulating a thyroglossal duct cyst: a case report. *Can J Surg* 1995;38:87–9.
- Fanaroff AA, Martin RJ, editors. *The respiratory system*. In: *Neonatal–perinatal medicine: diseases of the fetus and infant*, vol. 2. St Louis: Mosby; 1997. p. 1068.
- Ocampo-Candiani J, Villareal-Rodriguez A, Quinones-Fernandez AG, et al. Treatment of Fordyce spots with CO₂ laser. *Dermatol Surg* 2003;29:869–71.
- Warnke PH, Schimmelpenning GW, Happle R, et al. Intraoral lesions associated with sebaceous nevus syndrome. *J Cutan Pathol* 2006;33(2):175–80.
- Fitzgerald JF, Troncone R, Iwanczak F, et al. Clinical quiz. *J Pediatr Gastroenterol Nutr* 2004;38:151–3.
- Krajewska IA, Moore L, Brown LH. White sponge nevus presenting in the esophagus. Case report and literature review. *Pathology* 1992;24:112–15.
- Eisen D, Lynch D. Genodermatoses. In: *The mouth: diagnosis and treatment*. St Louis: Mosby; 1998. p. 193–4.
- Miller CS, Craig RM. White corrugated mucosa. *J Am Dental Assoc* 1988;117:345–7.
- Buley ID, Gatter KC, Kelly PM, et al. Granular cell tumors revisited. An immunohistochemical and ultrastructural study. *Histopathology* 1988;12:263.
- Junquera LM, deVincente JC, Vega JA, et al. Granular-cell tumours: an immunohistochemical study. *Br J Oral Maxillofac Surg* 1997;35:180–4.
- Bilen TB, Alaybeyoglu N, Arsian A, et al. Obstructive congenital granular cell tumor. *Int J Pediatr Otorhinolaryngol* 2004;68:1567–71.
- Noonan JD, Horton CE, Old WL, et al. Granular cell myoblastoma of the head and neck. *Am J Surg* 1979;138:611–14.
- Peterson LJ. Granular-cell tumor: review of the literature and report of a case. *Oral Surg* 1974;37:728–35.
- Robinson HBG, Miller AS, editors. *Colby, Kerr and Robinson's color atlas of pathology*. St Louis: JB Lippincott; 1990. p. 149.
- Brannon RB, Anand PM. Oral granular cell tumors: an analysis of 10 new pediatric and adolescent cases and a review of the literature. *J Clin Pediatr Dent* 2004;29:69–74.
- Reed RJ, Argenyi Z. Tumors of neural tissue. In: *Elder D, Elenitsas R, Jaworsky C, Johnson B, editors. Lever's histopathology of the skin*. 8th ed. Philadelphia: Lippincott-Raven; 1997. p. 994.
- Kershnik M, Batsakis JG, Mackay B. Granular cell tumors. *Ann Otol Rhinol Laryngol* 1994;103:416–19.
- Chrysomali E, Papanicolaou SI, Dekker NP, et al. Benign neural tumors of the oral cavity. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;84:381–90.
- Geist JR, Gander DL, Stefanac SJ. Oral manifestation of neurofibromatosis type I and II. *Oral Surg Oral Med Oral Pathol* 1992;73:376–82.
- Pouloupoulos AK, Antoniadis DZ, Epivatianos A, et al. Black hairy tongue in a 2-month-old infant. *J Paediatr Child Health* 2008;44(6):377–9.
- Yamashita T, Ito M, Taniguchi A, et al. Prevalence of coxsackievirus A5, A6, and A 10 in patients with herpangina in Aichi Prefecture, 2005. *Jpn J Infect Dis* 2005;58(6):390–1.
- Sinal SH, Woods CR. Human papillomavirus infections of the genital and respiratory tracts in young children. *Semin Pediatr Infect Dis* 2005;16(4):306–16.
- Hawkes M, Campisi P, Zafar R, et al. Time course of juvenile onset recurrent respiratory papillomatosis caused by human papillomavirus. *Pediatr Infect Dis J* 2008;27(2):149–54.
- Koskimaa HM, Waterboer T, Pawlita M, et al. Human papillomavirus genotypes present in the oral mucosa of newborns and their concordance with maternal cervical human papillomavirus genotypes. *J Pediatr* 2012;160(5):837–43.
- Orlow SJ, Isakoff MS, Blei F. Increased risk of symptomatic hemangiomas of the airway in association with cutaneous hemangiomas in a 'beard' distribution. *J Pediatr* 1997;131:643–6.
- O TM, Alexander RE, Lando T, et al. Segmental hemangiomas of the upper airway. *Laryngoscope* 2009;119(11):2242–7.
- Léauté-Labrèze C, Dumas de la Roque E, Hubiche T, et al. Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008;358(24):2649–51.
- Kwon EK, Seefeldt M, Drolet BA. Infantile hemangiomas: an update. *Am J Clin Dermatol* 2013;14(2):111–23.
- Eisen D, Lynch D. Developmental disorders. In: *The mouth: diagnosis and treatment*. St Louis: Mosby; 1998. p. 48.
- Shafer WG, Hine MK, Levy BM, editors. *Benign and malignant tumors of the oral cavity*. In: *A textbook of oral pathology*. 4th ed. Philadelphia: WB Saunders; 1983. p. 159–60.
- Stal S, Hamilton S, Spira M. Hemangiomas, lymphangiomas, and vascular malformations of the head and neck. *Otolaryngol Clin North Am* 1986;19:769–884.
- Levin SL, Jorgensen RJ, Jarvey BA. Lymphangiomas of the alveolar ridges in neonates. *Pediatrics* 1976;58:881–4.
- Burrows PE, Mitri RK, Alomari A, et al. Percutaneous sclerotherapy of lymphatic malformations with doxycycline. *Lymphat Res Biol* 2008;6(3–4):209–16.
- Rautio R, Keski-Nisula L, Laranne J, et al. Treatment of lymphangiomas with OK-432 (Picibanil). *Cardiovasc Intervent Radiol* 2003;26:31–6.
- Edwards PD, Rahbar R, Ferraro NF, et al. Lymphatic malformation of the lingual base and oral floor. *Plast Reconstr Surg* 2006;115:1906–15.
- Hebert AA, Lopez MC. Oral lesions in pediatric patients. In: *Advances in dermatology*, vol. 12. St Louis: Mosby; 1997. p. 181.
- Grevelink SV, Mulliken JB. Vascular anomalies. In: *Frederick IM, Eisen AZ, Wolff K, et al, editors. Fitzpatrick's dermatology in general medicine*. 5th ed. New York: McGraw-Hill; 1999. p. 1175–94.
- Dowling MB, Zhao Y, Darrow DH. Orofacial manifestations of facial port-wine stains. *J Am Acad Dermatol* 2012;67(4):687–93.
- Tay YK, Weston WL, Morelli JG. Treatment of pyogenic granuloma in children with the flashlamp-pumped pulsed dye laser. *Pediatrics* 1997;99:368–70.
- Okoro PE, Akadir OA. Giant macroglossia with persistent nonocclusion in a neonate. *Afr J Paediatr Surg* 2011;8(2):229–31.
- Bodenhoff J. Dentitio connatalis et neonatalis. *Odont Tidskr* 1959;67:645–95.
- Kates GA, Needleman HL, Holmes LB. Natal and neonatal teeth: a clinical study. *J Am Dent Assoc* 1984;109:441–3.
- Zhu J, King D. Natal and neonatal teeth. *J Dent Child* 1995;3:123–8.
- El Khatib K, Abouchadi A, Nassih M, et al. Neonatal teeth: study of five cases. *Rev Stomatol Chir Maxillofac* 2005;106:325–7.
- Nelson WE, editor. *Disorders of the teeth associated with other conditions*. In: *Nelson's textbook of pediatrics*. Philadelphia: WB Saunders; 1996. p. 1039.
- Eichenfield LF, Honig PJ, Nelson L. Traumatic granuloma of the tongue (Riga-Fede disease):

- association with familial dysautonomia. *J Pediatr* 1990;116:742–4.
64. Costacurta M, Maturro P, Docimo R. Riga–Fede disease and neonatal teeth. *Oral Implantol (Rome)* 2012;5(1):26–30.
65. Cohen RL. Clinical perspectives on premature tooth eruption and cyst formation in neonates. *Pediatr Dermatol* 1984;1:301–6.
66. Shafer WG, Hine MK, Levy BM, editors. Developmental disturbance of oral and paraoral structures. In: *A textbook of oral pathology*. 4th ed. Philadelphia: WB Saunders; 1983. p. 64.
67. Baroni A, Caprsito C, Rossiello L, et al. Lingual traumatic ulceration (Riga–Fede disease). *Inter J Dermatol* 2006;45(9):1096–7.
68. Maheswari NU, Kumar BP, Karunakran, et al. 'Early baby teeth': Folklore and facts. *J Pharm Bioallied Sci* 2012;4(Suppl 2):S329–33.
69. Iregbulem LM. Congenital lower lip sinuses in Nigerian children. *Br J Plast Surg* 1997;50:649–50.
70. Ranta A, Rintala A. Correlations between microforms of the van der Woude syndrome and cleft palate. *Cleft Palate J* 1983;20:158–62.
71. Lam AK, David DJ, Townsend GC, et al. Van der Woude syndrome: dentofacial features and implications for clinical practice. *Aust Dent J* 2010;55(1):51–8.
72. Mohrenschlager M, Kohler LD, Vogt HJ, et al. Congenital lower lip pits – a very rare syndrome? Report of two cases and review of the literature. *Cutis* 1998;61:127–8.
73. Velez A, Gorslay M, Buchner A, et al. Congenital lower lip pits (Van der Woude Syndrome). *J Am Acad Dermatol* 1995;3:520–1.
74. Capon-Degardin N, Martinot-Duquennoy V, Auvray G, et al. *Eur J Pediatr Surg* 2003;13:92–6.
75. Field M, Scheffer IE, Gill D, et al. Expanding the molecular basis and phenotypic spectrum of X-linked Joubert syndrome associated with OFD1 mutations. *Eur J Hum Genet* 2012;20:806–9.
76. Thauvin-Robinet C, Cossee M, Cormier-Daire V, et al. Clinical, molecular, and genotype–phenotype correlation studies from 25 cases of oral–facial–digital syndrome type 1: A French and Belgian collaborative study. *J Med Genet* 2006;43:54–61.
77. Larralde de Luna M, Raspa ML, Ibargoyen J. Oral–facial–digital type I syndrome of Papillon–Leage and Psaume. *Pediatr Dermatol* 1992;9:52–6.
78. Patrizi A, Orlandi C, Neri I, et al. What syndrome is this? Oral–facial–digital type I. *Pediatr Dermatol* 1999;16:329–31.
79. Kwong PC, O'Marcaigh AS, Howard R, et al. Oral and genital ulceration: a unique presentation of immunodeficiency in Athabaskan-speaking American Indian children with severe combined immunodeficiency. *Arch Dermatol* 1999;135:927–31.
80. Ghosal SP, Gupta PC, Muhherjee AK. Noma neonatorum: Its aetiopathogenesis. *Lancet* 1978;2:289–90.
81. Juster-Reicher A, Mogilner BM, Levi G, et al. Neonatal noma. *Am J Perinatol* 1993;10:409–11.
82. Chang YS, Yang YH, Chiang BL. Neonatal Behçet's disease without maternal history. *Clin Rheumatol* 2011;30(12):1641–5.
83. Fain O, Mathieu E, Lachassinne E, et al. Neonatal Behçet's disease. *Am J Med* 1995;98:310–11.
84. Jog S, Patole S, Koh G, et al. Unusual presentation of neonatal Behçet's disease. *Am J Perinatol* 2001;18:287–91.
85. Stark AC, Bhakta B, Chamberlain MA, et al. Life threatening transient neonatal Behçet's disease. *J Rheumatol* 1997;36:700–2.
86. Kaklamani V, Vaiopoulos G, Kaklamani PG. Behçet's disease. *Semin Arthritis Rheum* 1998;27:197–217.
87. Ogata M. Acatalasemia. *Hum Genet* 1991;86:331–40.
88. Dohil MA, Billman G, Pransky S, et al. The congenital lingual melanotic macule. *Arch Dermatol* 2003;139:767–70.
89. Amir E, Gorsky M, Buchner A, et al. Physiologic pigmentation of the oral mucosa in Israeli children. *Oral Surg Med Oral Pathol* 1991;71:396–8.
90. Cambiaghi S, Colonna C, Caballi R. Geographic tongue in two children with non-pustular psoriasis. *Pediatr Dermatol* 2005;22:83–5.
91. Yilmaz AE, Gorpelioglu C, Sarifakioglu E, et al. Prevalence of oral mucosal lesions from birth to two years. *Niger J Clin Pract* 2011;14(3):349–53.
92. Eroglu E, Yip M, Oktar T, et al. How should we treat prepubertal labial adhesions? Retrospective comparison of topical treatments: estrogen only, betamethasone only, and combination estrogen and betamethasone. *J Pediatr Adolesc Gynecol* 2011;24(6):389–91.
93. Leung AK, Robson WL, Tay-Uyboco J. The incidence of labial fusion in children. *J Paediatr Child Health* 1993;29:235–6.
94. Starr NB. Labial adhesions in childhood. *J Paediatr Child Health* 1996;10:26–7.
95. Kayashima K, Kitoh M, Ono T. Infantile perianal pyramidal protrusion. *Arch Dermatol* 1996;132:1481–4.
96. Merigou D, Labreze C, Lamireau T, et al. Infantile perianal pyramidal protrusion: A marker of constipation? *Pediatr Dermatol* 1998;15:143–4.
97. Cruces MJ, DeLaTorre C, Losada A, et al. Infantile pyramidal protrusion as a manifestation of lichen sclerosis et atrophicus. *Arch Dermatol* 1998;134:1118–20.
98. Fleet SL, Davis LS. Infantile perianal pyramidal protrusion: Report of a case and review of the literature. *Pediatr Dermatol* 2005;22:151–2.
99. Miyamoto T, Inoue S, Hagari Y, et al. Clinical cameo: infantile perianal pyramidal protrusion with hard stool history. *Br J Dermatol* 2004;151:229.
100. Stephens FD. The female anus, perineum and vestibule: Embryogenesis and deformities. *Aust NZ J Obstet Gynaecol* 1968;8:55.
101. Verma SB, Wollina U. Perineal groove – A care report. *Pediatric Dermatol* 2010;27(6):626–7.
102. Esposito C, Giurin I, Salvaneli A, et al. Current trends in the management of pediatric patients with perineal groove. *J Pediatr Adolesc Gynecol* 2011;24:263–5.
103. Sekara P, Shawis R. Perineal groove: A rare congenital abnormality of failure of fusion of the perineal raphe and discussion of its embryological origin. *Clin Anat* 2009;22:823–5.
104. Berenson AB, Heger A, Andrews S. Appearance of the hymen in newborns. *Pediatrics* 1991;87(4):458–65.
105. Berenson AB. A longitudinal study of hymenal morphology in the first 3 years of life. *Pediatrics* 1995;95(4):490–6.
106. Berenson AB. Appearance of the hymen at birth and one year of age: a longitudinal study. *Pediatrics* 1993;91(4):820–5.
107. Yaffe D, Zissin R. Cowper's glands duct: radiographic findings. *Urol Radiol* 1991;13:123–5.
108. Pieretti RV, Goldstein AM, Pieretti-Vanmarcke R. Late complications of newborn circumcision: a common and avoidable problem. *Pediatr Surg Int* 2012;26:515–18.
109. Ponsky LE, Ross JH, Knipper N, et al. Penile adhesions after neonatal circumcision. *J Urol* 2000;164:495–6.
110. Becker K. Lichen sclerosis in boys. *Dtsch Arztebl Int* 2011;108(4):53–8.
111. Graham JA, Hansen KK, Rabinowitz LG, et al. Pyoderma gangrenosum in infants and children. *Pediatr Dermatol* 1994;11:10–17.
112. Edwards BM, Kileny PR, Van Riper LA. CHARGE syndrome: a window of opportunity for audiologic intervention. *Pediatrics* 2002;110:119–26.
113. Calhoun JH. Problems of the lacrimal system in children. *Pediatr Clin North Am* 1987;34:1457–65.
114. Hurwitz S. Eczematous eruptions in childhood. In: *Clinical pediatric dermatology*. 4th ed. Philadelphia: WB Saunders; 2011. p. 37–70.
115. Chamaillard M, Mortemousque B, Boralevi F, et al. Cutaneous and ocular signs of childhood rosacea. *Arch Dermatol* 2008;144(2):167–71.
116. Henningsen E, Bygum A. Budesonide-induced periorificial dermatitis presenting as chalazion and blepharitis. *Pediatr Dermatol* 2011;28(5):596–7.
117. Rao VA, Baskaran RK, Krishnan MM. Unusual cases of molluscum contagiosum of eye. *Indian J Ophthalmol* 1985;33(4):263–5.
118. Martyn LJ, DiGeorge A. Pediatric ophthalmology. *Pediatr Clin North Am* 1987;34:1530–6.
119. Tellier AL, Cormier-Daire V, Abadie V, et al. CHARGE syndrome: Report of 47 cases and review. *Am J Med Genet* 1998;76:402–9.
120. Searle LC, Graham JM Jr, Prashad C, et al. CHARGE syndrome from birth to adulthood: An individual reported on from 0 to 33 years. *Am J Med Genet A* 2005;133:344–9.

Introduction

This chapter covers neonatal hair patterns, genetic hair shaft abnormalities, and the conditions in which hypo- or hypertrichosis are present in the neonatal period. There are many syndromes in which hypotrichosis or atrichia occur, and those in which it is a prominent feature are discussed. Localized alopecia can occur physiologically, with trauma, and as a nevus disorder, either alone or associated with other nevi. Diffuse hypertrichosis can occur alone or as part of various syndromes. Localized hypertrichosis may occur with other nevi, but also may be a marker for serious neural tube closure defects (see also Chapter 9).

Neonatal hair development

The hair root is characterized by three definable stages of growth: anagen, catagen, and telogen.

The anagen stage is a growth phase that may last for many years. The catagen stage is a brief transition from the growth phase (anagen) to an inactive state. The telogen stage is the resting phase following catagen and lasts approximately 3 months. In adults, each region of the scalp contains hairs in different phases of the hair cycle.

In the fetus, hair follicles appear at about 10 weeks' gestation and by 20 weeks' gestation, all the hair on the scalp is in anagen phase. At about 30 weeks' gestation, the hair in the frontal and parietal region rapidly transition through a catagen and telogen phase, representing the first shedding for the fetus. At or just before birth, scalp hair grows in synchronized waves, starting with the hairs in the frontal and parietal regions and ending with the occipital region. Hair density, structure, and growth vary depending on sex, ethnicity and nutritional status. From the 18th week after birth, changes in growth patterns progressively adopt the dyssynchronous pattern of the adult scalp.¹⁻³

Scalp hair whorls

The sloping angle of scalp hair results from stretch on the scalp from the growth of the underlying fetal brain during weeks 10–16 of gestation. The usual location of the parietal hair whorl is several centimeters anterior to the posterior fontanelle. Of normal Caucasian infants, 95–98% have a single hair whorl in the parietal area,^{4,5} usually clockwise but inconsistent in position. The remainder have a double parietal whorl. Only 10% of African-American individuals with short curly hair have a parietal whorl.⁵ A mild frontal upsweep or 'cowlick' is present in 7% of normal infants.⁴ Hair patterns may be very abnormal in infants with structural abnormalities of the brain, demonstrating a striking frontal upsweep and absent or aberrant parietal whorls.⁴ Multiple parietal whorls occur with increased

frequency in developmentally delayed children, and their presence in the neonate may be an early sign of such a disorder.⁶ A recent study of hair whorl orientation and handedness suggests that a single gene controls these traits.⁷

The hairline

The frontal hairline of neonates is lower than in older children, a feature most striking in racial groups in which there is profuse hair at birth. These terminal hairs on the brow are gradually replaced over the first 12 months of life by vellus hairs. Normally, posterior hairline hair roots are located above the neck crease. Low frontal and posterior hairlines are each associated with several syndromes, summarized in Box 31.1.

Heterochromia of scalp hair

Heterochromia of the hair is described as the growth of hair with two distinct colors in the same person.⁸ In piebaldism, there is a white forelock, which will be obvious in a dark-haired neonate. A congenital melanocytic nevus may present as a tuft of dark hair, which is often also longer and coarser than the surrounding normal hair. In hereditary, usually autosomal dominant, heterochromia, there may be a tuft of red hair in a dark-haired neonate or a dark tuft in a fair individual. There has recently been a report of a diffuse heterochromia of scalp hair, present from birth, with black and red hairs evenly distributed over the scalp⁸ and heterochromia of the scalp hair following Blaschko's lines.⁹

Hair shaft abnormalities

A diverse group of conditions can result in hair shaft abnormalities. Some are associated with extracutaneous disease, whereas others affect only the hair itself. These conditions have been reviewed in detail by Whiting,¹⁰ Price,¹¹ and Rogers.^{12,13}

Trichoscopy performed with a handheld dermoscope or a video-dermoscope is becoming a useful tool in the diagnosis of hair shaft disorders.¹⁴

MONILETHRIX

Monilethrix is a condition that produces a beaded appearance of the hair and the term comes from the Latin word for necklace (*monile*) and the Greek for hair (*thrix*).¹⁰⁻¹² Most families with monilethrix show an autosomal dominant inheritance pattern, but autosomal recessive forms also exist. The hair is usually normal at birth but is replaced within weeks by affected hairs that are dry, dull, and brittle, breaking spontaneously and leaving a stubble-like appearance (Fig. 31.1). The hairs may break almost flush with the scalp or may attain lengths of

BOX 31.1 SYNDROMES ASSOCIATED WITH ABNORMAL HAIRLINES

LOW FRONTAL HAIRLINE:

- Costello syndrome
- Cornelia de Lange (Brachmann–de Lange) syndrome
- Coffin–Siris syndrome
- Diamond–Blackfan anemia
- Fanconi syndrome
- Saethre–Chotzen syndrome
- Fetal hydantoin syndromes

LOW POSTERIOR HAIRLINE:

- Noonan syndrome
- Turner syndrome
- Kabuki syndrome
- Cornelia de Lange (Brachmann–de Lange) syndrome
- Klippel–Feil anomaly
- Fetal hydantoin syndrome



Figure 31.1 Monilethrix. Follicular plugging and short, broken hairs.

0.5–2.5 cm, or occasionally longer. There may be spontaneous improvement with time, especially during puberty and pregnancy, but the condition never resolves completely. Follicular keratosis is commonly associated and may involve the scalp, face, and limbs. On microscopy, spindle-shaped ‘nodes’ separated by constricted internodes are seen (Fig. 31.2). The nodes have the diameter of normal hair and may be medullated, whereas the internodes are narrower and usually nonmedullated, and are the sites of fracture. In monilethrix the hair shaft fragility is due to structural weakness of the hair fiber that is caused by a genetic defect in keratin intermediate filament protein. Mutations in the hair cortex keratin genes *KRT81* (hHB1), *KRT83* (hHB3), and *KRT86* (hHB6) have been identified in autosomal dominant monilethrix.¹⁵ An autosomal recessive form of monilethrix is caused by mutation in the *DSG4* gene and presents with more extensive alopecia of the scalp, body, and limbs, and a papular rash involving the extremities and periumbilical region.¹⁶



Figure 31.4 Pili torti in Menkes syndrome.

PILI TORTI

This is characterized by groups of three or four regularly spaced twists of the hair shaft on its own axis (Fig. 31.3).^{9,10} Microscopically, twists are seen, each 0.4–0.9 mm in width, occurring usually in groups of three or more at irregular intervals. Twists are almost always 180°, although some are 90° or 360°. The hair shaft is somewhat flattened. Pili torti may occur as an isolated phenomenon, with onset at birth or in the early months of life. The hair is usually fairer than expected and is spangled, dry, and brittle, breaking at different lengths (Fig. 31.4). It may stand out from the scalp and tends to be short, especially in areas subject to trauma.

Pili torti can occur alone or as a manifestation of defined syndromes, some of which are identifiable in the neonatal period. Menkes syndrome is an X-linked recessive condition caused by mutations in a gene encoding for a protein believed to be a copper-transporting P-type ATP-ase,¹⁷ and the multiple abnormalities are due to decreased bioavailability of copper, with resultant functional deficiencies of copper-dependent enzymes. In the early months of life, scalp and eyebrow hair becomes kinky, coarse, and sparse. Lax, pale skin, hypotonia, and early neurodegenerative changes may already be seen in the neonatal period. In Bazex syndrome, inherited as an X-linked dominant trait,¹⁸ congenital hypotrichosis with pili torti is associated with follicular atrophoderma and multiple facial milia, both of which may also be present from birth. These patients have an increased susceptibility to the development of basal cell carcinomas. In Björnstad syndrome, pili torti is associated with sensorineural deafness and occasionally mental retardation.¹⁹ In later childhood, normal hair may replace the affected hairs, with a considerable improvement in appearance. Both autosomal dominant and recessive inheritance patterns have been reported. Recently the gene for Björnstad syndrome has been mapped to chromosome 2 in a family with an autosomal recessive mode of inheritance (Fig. 31.5).¹⁹ Pili torti may occur also in Rapp–Hodgkin syndrome, although pili canaliculi is the more characteristic finding.

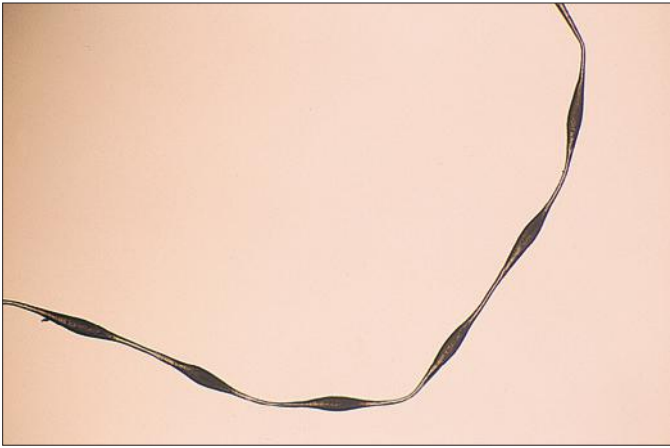


Figure 31.2 Monilethrix. Microscopic appearance.



Figure 31.3 Pili torti. Electron microscopic appearance.



Figure 31.5 Pili torti in Björnstad syndrome.

BOX 31.2 CONDITIONS ASSOCIATED WITH TRICHORRHEXIS NODOSA

- Netherton syndrome
- Trichohepatoenteric syndrome
- Tay syndrome
- Trichorrhexis nodosa syndrome (Pollitt syndrome)
- Argininosuccinic aciduria
- Menkes disease
- Biotin deficiency (uncommonly seen)
- Trichodysplasia xeroderma
- Autosomal recessive hypotrichosis (DSG4 and PLAR6 mutations)
- Pili torti
- Autosomal dominant woolly hair
- Autosomal dominant oculodentodigital dysplasia
- Congenital disorder of glycosylation type Ia
- Cataract-alopecia-sclerodactyly syndrome



Figure 31.7 Short, broken, dull hair in trichothiodystrophy.

TRICHORRHEXIS NODOSA

The term trichorrhexis nodosa (TN) refers to the light microscopic appearance of a fracture with splaying out and release of individual cortical cells from the main body of the hair shaft, producing an appearance suggestive of the ends of two brushes pushed together (Fig. 31.6).^{10–12} When the break occurs, the brush-like end is clearly seen. Electron microscopy shows the disrupted cuticle and splaying of cortical cells. The defect renders the hair very fragile, and it breaks readily with trauma – or sometimes probably spontaneously. In congenital autosomal dominant TN, the hair is usually normal at birth but is replaced within a few months with abnormal, fragile hair. Trichorrhexis nodosa was found in eight of 25 children with mitochondrial disorders in the absence of skin manifestations, suggesting that hair examination may be a useful diagnostic tool when these disorders are suspected.²⁰ Trichorrhexis nodosa is also seen in trichohepatoenteric syndrome, a condition that includes intractable diarrhea of infancy, facial dysmorphism, developmental delay, and immunodepression.²¹

There is a growing list of conditions associated with trichorrhexis nodosa (Box 31.2).

TRICHOThIODYSTROPHY

The term ‘trichothiodystrophy’ refers to the sulfur-deficient brittle hair that is a marker for a neuroectodermal symptom complex occurring in a group of autosomal recessive genetic disorders.²² There is considerable genetic heterogeneity in trichothiodystrophy.²³ Named syndromes that fit into this spectrum include: Tay, Pollitt, Sabinas brittle hair, and Marinesco–Sjögren syndromes. The major clinical features seen in this group of conditions are photosensitivity with a DNA repair defect (due to mutations in the *XPD ECCR2* DNA repair/transcription gene), ichthyosis, brittle hair, intellectual impairment, decreased fertility, short stature,^{24–26} and osteosclerosis. Some authors use mnemonic acronyms including PIBIDS, IBIDS, and BIDS to identify patients by these key clinical characteristics (see also Chapter 19).²³ Features that may be evident in the neonatal period are intrauterine growth retardation, severe infections, congenital cataracts, nail dystrophy, facial dysmorphism, a collodion baby phenotype, and the characteristic fragile, dull, short, disordered hair involving the scalp hair, eyebrows, and eyelashes (Fig. 31.7).^{27,28} On light microscopy the

hair has a wavy, irregular outline and a flattened shaft, in which twists like a folded ribbon occur. Two types of fracture are seen: an atypical trichorrhexis nodosa and trichoschisis, a clean, transverse fracture (Fig. 31.8A). Using crossed polarizers, light and dark bands are seen when the hair is aligned in one of the polarizer directions – the so-called tiger-tail appearance (Fig. 31.8B). This may be absent at birth and is not fully developed until 3 months of age.²⁹ Scanning electron microscopy shows irregular ridging and fluting and a disordered, reduced, or absent cuticle scale pattern.

WOOLLY HAIR

Woolly hair (WH) is an abnormal variant of tightly curled hair. Compared with normal curly hair, WH does not grow well and stops growing at a few inches.

Several families have been reported in which some affected individuals exhibit features of hypotrichosis while others have woolly scalp hair.³⁰

Clinically, WH can be divided into syndromic and non-syndromic forms. The syndromic form includes Naxos disease, cardiofaciocutaneous syndrome and Carvajal syndrome.

Naxos disease is an autosomal recessive disorder that combines palmoplantar keratoderma and other ectodermal features with arrhythmic right ventricular dysplasia/cardiomyopathy. It was first reported in families on the Greek island of Naxos and is associated with a deletion in the plakoglobin gene. Cardiofaciocutaneous (CFC) syndrome is characterized by a distinctive facial appearance, heart defects, and mental retardation and is caused by heterozygous gain-of-function mutations in one of four different genes: *KRAS*, *BRAF*, *MEK1*, or *MEK2*. Some patients have associated woolly hair. In Carvajal syndrome, patients present with epidermolytic palmoplantar keratoderma, woolly hair, and dilated cardiomyopathy. Carvajal syndrome can be caused by mutations in the gene encoding desmoplakin.^{31–36}

Non-syndromic forms of hereditary woolly hair present as autosomal dominant (ADWH) or autosomal recessive (ARWH). Dominant forms of WH have been linked to mutations in the helix initiation motif of *KRT74*. Recessive forms of WH have been linked to mutations in the *LIPH* and the *LPAR6/P2RY5* genes, both expressed in the inner root sheath of the hair follicle.

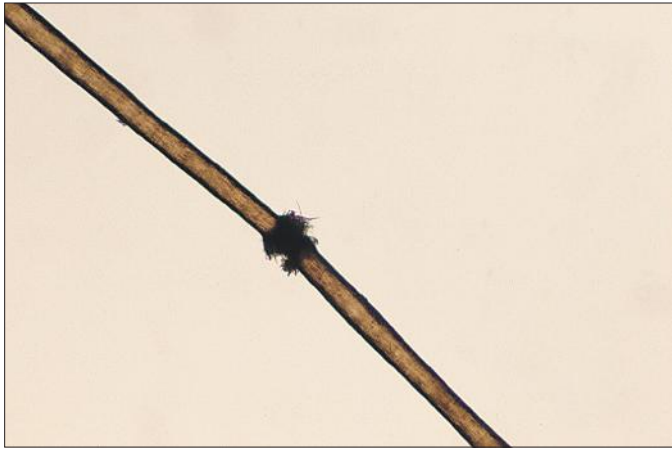


Figure 31.6 Trichorrhexis nodosa. Light microscopic appearance.

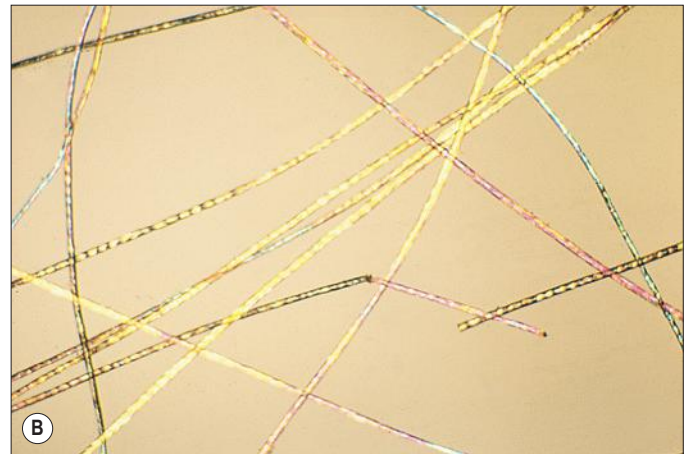


Figure 31.8 (A) Trichoschisis in trichothiodystrophy. Light microscopic appearance. (B) 'Tiger tail' appearance of light and dark bands on polarizing microscopy of hair in trichothiodystrophy.



Figure 31.9 Woolly hair.



Figure 31.10 Uncombable hair. Note the frizzy quality and orientation away from the scalp. (Courtesy of Dr Angela Hernandez-Martin.)

Localized and sporadic woolly hair (the woolly hair nevus) (Fig. 31.9) can also occur.

UNCOMBABLE HAIR

Uncombable hair is a relatively rare anomaly of the hair shaft that results in a disorganized, unruly hair pattern that is impossible to comb flat.^{11,13,37} Synonyms are spun-glass hair, pili canaliculi, and pili trianguli et canaliculi. In the classic clinical form, the hair is a light silvery-blond, paler than expected. It is frizzy, stands away from the scalp, and cannot be combed flat. It is often 'spangled' or glistening (Fig. 31.10). It is usually normal in length, quantity, and tensile strength. The onset may be with the first terminal growth or later. Eyebrows, lashes, and body hair are normal. Most cases improve with the onset of puberty. There are reports suggesting both dominant and recessive inheritance patterns. Scanning electron microscopy best demonstrates the characteristic shallow grooving or flattening of the surface.³⁷ These areas are often discontinuous and change orientation many times along the length of the hair, occurring on



Figure 31.11 Absence of scalp hair, scale, and erythroderma in a neonate with Netherton syndrome.

different planes of the hair at different points. Cross-sectional microscopy shows triangular, reniform, and other unusual shapes. Most children with uncombable hair are otherwise normal; the findings have been demonstrated in a variety of other syndromes with congenital onset, including progeria, Marie Unna hypotrichosis,³⁸ Rapp–Hodgkin syndrome,³⁹ orofacial digital syndrome type I,⁴⁰ ectrodactyly ectodermal dysplasia and clefting syndrome,⁴⁰ and hypohidrotic ectodermal dysplasia.³⁹ The classic clinical appearance of spun-glass or uncombable hair would seem to depend on the proportion of abnormal hairs.

PILI ANNULATI

This hair shaft abnormality, which may be present at birth, does not result in significant hair fragility. The hair looks pleasantly shiny, and on close observation alternating bright and dark bands are seen.⁴¹ There are usually no associated abnormalities. The condition may be sporadic or inherited, usually as a dominant characteristic. The bright areas are due to light scattered from clusters of air-filled cavities within the cortex, and in a hair mount, viewed with transmitted light, the light areas appear as dark patches. Scanning electron microscopy shows longitudinal wrinkling and folding in bands corresponding to the abnormal areas, possibly due to the evaporation of air in the spaces when the hair is coated in the vacuum. Transmission electron microscopy demonstrates multiple holes within the cortex. Recently, a locus for pili annulati was mapped to Ch12q24.32–24.33.⁴²

TRICHORRHEXIS INVAGINATA

This is the characteristic hair shaft abnormality of Netherton syndrome, an autosomal recessive condition due to mutations in the *SPINK5* gene, which encodes for the serine protease inhibitor *LEKTI* (see also Chapter 19).⁴³ Although the severity varies considerably, the clinical and microscopic findings are present from birth. In the severely affected neonate, the hair may be extremely sparse or even absent altogether (Fig. 31.11). What hair is present is short and dull and breaks easily. The changes may affect eyebrows, eyelashes, and general body hair.¹³

Hair mount demonstrates a ball-and-socket configuration with various patterns seen (Fig. 31.12). The classic 'bamboo

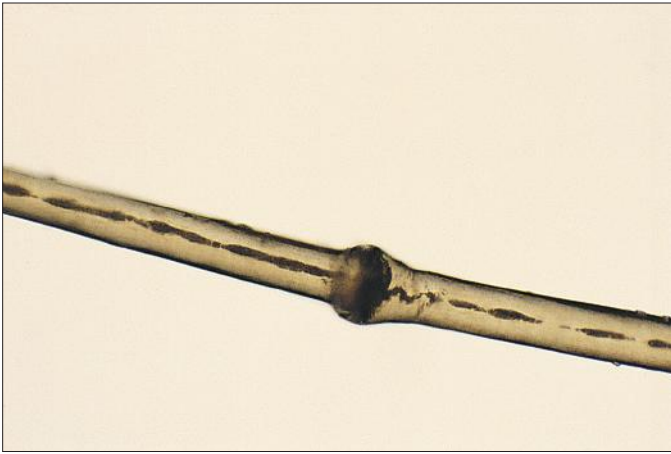


Figure 31.12 Trichorrhexis invaginata in Netherton syndrome.
Light microscopic appearance.

hair' occurs when the soft abnormal hair shaft wraps around a firmer distal shaft, producing the appearance of a shallow invagination of the distal into the proximal shaft. There is a tulip-like form with a deeper invagination and longer sides of the 'cup'.¹¹ Circumferential strictures may be found, representing the earliest stage of the invagination. The term 'golf-tee hair' has been given to the expanded proximal end of an invaginate node after a break has occurred. Thin vellus hairs may show multiple invaginations, the so-called 'canestick hairs'.⁴⁴ A helical pattern of twisting with obliquely running parallel invaginations has recently been described.⁴⁵

Diffuse alopecia (hypotrichosis) (Box 31.3)

HYPOTRICHOSIS WITH HAIR SHAFT ABNORMALITIES

As discussed in the previous section, many hair shaft abnormalities present in the neonatal period or in early infancy with significant hypotrichosis.

ISOLATED CONGENITAL ALOPECIA OR HYPOTRICHOSIS WITHOUT OTHER DEFECTS

There appear to be several distinct genotypes within this group, with recessive, dominant, and X-linked inheritance patterns being represented.^{46,47}

Those with recessive inheritance are in general the most severe and congenital in onset. In some pedigrees, there is a total absence of hair (congenital atrichia, atrichia congenita, alopecia universalis congenita) and on biopsy no hair follicles are found.

BOX 31.3 DIFFUSE ALOPECIA OR HYPOTRICHOSIS

- Hypotrichosis with major hair shaft abnormalities
- Congenital alopecia or hypotrichosis without other defects
- Atrichia congenita
- Congenital hypotrichosis
- Marie Unna hypotrichosis
- Atrichia with papular lesions
- Congenital hypotrichosis and milia
- Hypotrichosis with juvenile macular dystrophy
- Hypotrichosis–lymphedema–telangiectasia syndrome
- Hypotrichosis in ectodermal dysplasias
 - Hidrotic ectodermal dysplasia
 - Hypohidrotic ectodermal dysplasia
 - Anhidrotic ectodermal dysplasia with immunodeficiency
 - Ankyloblepharon ectodermal dysplasia and clefting syndrome and Rapp–Hodgkin syndrome
 - Bazex–Dupré–Christol syndrome
 - Congenital atrichia with nail dystrophy, abnormal facies and retarded psychomotor development
 - Ectodermal dysplasia/skin fragility syndrome
- Hypotrichosis with ichthyoses
 - Ichthyoses presenting as the collodion baby phenotype
 - Congenital ichthyosis, follicular atrophoderma, hypotrichosis and hypohidrosis
 - Keratitis, ichthyosis and deafness syndrome
 - Ichthyosis follicularis, congenital atrichia and photophobia
- Hypotrichosis with hereditary mucoepithelial dysplasia
- Hypotrichosis with premature aging syndromes
- Hypotrichosis with immunodeficiency syndromes
- Loose anagen syndrome

Mutations in the *hairless* gene on chromosome 8 have been demonstrated in some families.⁴⁶

In some dominant pedigrees, the hair is present but extremely sparse (congenital hypotrichosis, hypotrichosis simplex), with biopsy demonstrating a few scattered, miniaturized follicles occurring in decreased numbers; only the scalp is involved, the hair elsewhere being normal. In some of these pedigrees mutations have been found in corneodesmosin, a keratinocyte adhesion molecule.⁴⁸

MARIE-UNNA HYPOTRICHOSIS

The hair in this autosomal dominant condition is usually sparse or absent at birth, but it is not until early childhood that the characteristic coarse, wiry hair appears, showing flattening and irregularly distributed twisting on microscopy.^{49,50} The condition has been mapped to a mutation in the inhibitory upstream open reading frame of the *hairless* gene on chromosome 8p21.^{51,52}

ATRICHIA WITH PAPULAR LESIONS

This is a distinctive association of congenital atrichia and tiny, white papules.⁵³ Atrichia of the scalp may be present from birth or appear in early childhood. In most cases, fetal hair is shed in the first 3 months of life and never replaced; eyebrows and eyelashes may or may not be involved (Fig. 31.13). The papular lesions, which occur diffusely but predominate on the face and scalp, are not present in the neonatal period. Histopathology shows the papules to represent keratin-filled follicular cysts in contact with the overlying epidermis. Recent work has demonstrated mutations in the *hairless* gene on chromosome 8, as seen also in alopecia universalis congenita.⁴⁷

Vitamin D-dependent rickets type 2A (VDDR2A) can present with alopecia that is clinically and pathologically indistinguishable from that seen in atrichia with papular lesions.⁵⁴

CONGENITAL HYPOTRICHOSIS AND MILIA

In this condition, which bears some clinical similarity to atrichia with papular lesions, there is hypotrichosis with sparse, coarse hair, and multiple milia are present at birth on the face and



Figure 31.13 Nearly universal alopecia in a patient with atrichia with papular lesions.

sometimes also the limbs and trunk. Study of a large pedigree suggests X-linked dominant inheritance.⁵⁵

HYPOTRICHOSIS WITH JUVENILE MACULAR DYSTROPHY

Hair that is short and sparse from birth is a feature of this rare autosomal recessive disorder in which progressive macular degeneration can lead to blindness during the first to fourth decades. The hair may be morphologically normal or show a variety of nonspecific shaft abnormalities. The disease results from mutations in *CDH3* encoding P-cadherin.⁵⁶

HYPOTRICHOSIS-LYPHHEDEMA-TELANGELECTASIA SYNDROME

Congenital hypotrichosis is a feature of this condition, accompanied later in life by lymphedema and telangiectasia. Mutations have been found in the transcription factor gene *SOX18*.⁵⁷

HYPOTRICHOSIS ASSOCIATED WITH ECTODERMAL DYSPLASIAS

Hypotrichosis (see also [Chapter 29](#)) is an important feature in many ectodermal dysplasias,⁵⁸ but often becomes obvious only after the neonatal period. A selection of conditions in which there may be congenital or early-onset severe hypotrichosis or atrichia will be considered here.

Hidrotic ectodermal dysplasia (Clouston syndrome)

Hypotrichosis of a variable and sometimes very severe degree of scalp hair, eyebrows, eyelashes, and body hair is usually present at birth.⁵⁹ Any hair present is fine and fragile. Later significant features are leukoplakia, nail dystrophy, and palmo-plantar keratoderma. The condition is caused by mutations in *GJB6*, coding connexin 30.⁵⁹ Rare cases of Clouston syndrome have sensorineural deafness which may represent a contiguous gene syndrome resulting from deletion of the *GJB6* gene and of the connexin-26 gene (*GJB2*).⁶⁰

Hypohidrotic ectodermal dysplasia

This condition may be inherited due to one of four defects: (1) the *EDA* gene, which encodes ectodysplasin-A on Xq13.1, leading to X-linked hypohidrotic ectodermal dysplasia (HED); (2) the ectodysplasin receptor (*EDAR*) on 2q12.3, with autosomal dominant and recessive forms; (3) the *EDAR* death domain (*EDARADD*) on 1q42-q43, with autosomal dominant and recessive forms; (4) the *NEMO* gene on Xq28, which presents with immunodeficiency, and occasionally osteopetrosis and lymphedema.⁶¹

The majority of cases represent a mutation in the *EDA* gene and are characterized by marked hypotrichosis of all hair-bearing areas, often evident in the neonatal period; hair that is present is fine and fair, and often shows pili canaliculi on microscopy. Other features that may be evident in the neonatal period include impaired heat regulation, diffuse scaling of skin, hypoplastic or absent nipples, and the typical facies with a depressed nasal bridge and prominent brow.⁶² Rouse and colleagues⁶³ reported that scalp biopsies from patients with hypohidrotic ectodermal dysplasia (HED) demonstrate an absence of eccrine structures in the majority of cases. Their absence is diagnostic of HED, and their presence suggests that the patient

does not have this disorder. As the eccrine apparatus is fully formed by the third trimester this test should be reliable in the neonate.⁶³

Ankyloblepharon, ectodermal dysplasia and clefting syndrome, and Rapp-Hodgkin syndrome

At birth in the ankyloblepharon, ectodermal dysplasia and clefting syndrome (AEC, Hay-Wells), the scalp is usually red and scaly with extensive erosions and crusts, and there is a severe hypotrichosis ([Fig. 31.14](#)).⁶⁴ Other neonatal features include a generalized erythroderma with or without erosive lesions, ankyloblepharon filiforme, lacrimal duct atresia, cleft palate and lip, and hypoplastic nails. Both Rapp-Hodgkin and AEC syndromes have mutations in 3q27 which encodes the *p63* gene. As such, they are currently viewed as related disorders, with reported cases of Rapp-Hodgkin syndrome sharing all the features of AEC apart from the ankyloblepharon.^{58,65}

Bazex-Dupré-Christol syndrome

The main features of this probably X-linked dominant condition are congenital hypotrichosis, milia with onset in the first 3 months of life, the later appearance of follicular atrophoderma as the milia are shed, and early development of basal cell carcinomas.¹⁸ Microscopic hair shaft examination may show trichorrhexis nodosa and an irregular twisting.

Congenital atrichia with nail dystrophy, abnormal facies, and retarded psychomotor development

In this condition, after the shedding in the first weeks of life of an initial sparse cover of hair, there is almost total alopecia with only tiny vellus hairs being evident; scalp biopsy demonstrates atrophy of hair follicles and rudimentary hair shafts.⁶⁶ Nail dystrophy and an abnormal facies with a broad nasal bridge, hypertelorism, a broad nose, and a long philtrum are other congenital features.

Ectodermal dysplasia/skin fragility syndrome

Mutations in the desmosomal protein plakophilin have been demonstrated in an ectodermal dysplasia with sparse hair, skin fragility, hypohidrosis, palmo-plantar keratoderma, and hyperkeratotic plaques elsewhere.^{49,58}



Figure 31.14 Scalp crusting and alopecia in ankyloblepharon-ectodermal dysplasia-clefting (AEC) syndrome.



Figure 31.15 Alopecia in neonate with lamellar ichthyosis.

HYPOTRICHOSIS ASSOCIATED WITH ICHTHYOSSES

Ichthyoses presenting as the collodion baby phenotype

In this group of conditions (see also [Chapter 19](#)), which includes autosomal recessive and autosomal dominant forms of lamellar ichthyosis, congenital ichthyosiform erythroderma, and lamellar ichthyosis of the newborn (self-healing collodion baby), the hair is often either absent or shed in the early weeks of life with the collodion scale ([Fig. 31.15](#)).

Congenital ichthyosis, follicular atrophoderma, hypotrichosis, and hypohidrosis

This combination of traits has been described as a new autosomal recessive genodermatosis.⁶⁷ Hypotrichosis of scalp, eyebrows, and eyelashes is evident in the neonatal period, and the ichthyosis and follicular atrophoderma are both also congenital. Woolly hair was an additional feature in one case.⁶⁷

Keratitis, ichthyosis, and deafness (KID) syndrome

Severe hypotrichosis of scalp, eyebrows, and eyelashes may be evident at birth ([Fig. 31.16](#)). Other congenital features include spiny follicular plugs, perioral furrowing, reticulate hyperkeratosis of the palms and soles, widespread thickened erythematous plaques, and hearing loss. The condition is usually caused by mutations in *GJB2*, encoding connexin 26.^{48,59}

Ichthyosis follicularis, congenital atrichia, and photophobia (IFAP)

From birth these individuals demonstrate keratotic follicular papules, atrichia, or severe hypotrichosis and photophobia.⁶⁸ A variety of other features can be present and there are pedigrees suggesting both X-linked recessive and autosomal dominant inheritance. Happle⁶⁹ suggests there may be more than one syndrome within this designation. A functional deficiency of a zinc metalloprotease causes the disease (MBTPS2).⁷⁰

HYPOTRICHOSIS WITH HEREDITARY MUCOEPITHELIAL DYSPLASIA

Hereditary mucoepithelial dysplasia is a dominantly inherited disease characterized by congenital nonscarring hypotrichosis



Figure 31.16 Alopecia and thick scale in keratitis-ichthyosis-deafness (KID) syndrome. (Courtesy of Dr Virginia Sybert.)

with coarse abnormal hair, gingival erythema, severe keratitis, follicular keratotic papules, and periorificial psoriasiform plaques.⁷¹ It has been suggested that this and IFAP may be the same condition, but there are sufficiently different features to make it likely they are separate entities. Searches for abnormal expression of gap junction and desmosomal proteins have so far been unrewarding.⁷¹

HYPOTRICHOSIS WITH PREMATURE AGING SYNDROMES

Although the onset of obvious hypotrichosis is often delayed until several years of age in these conditions, in some cases of Hutchison-Gilford progeria, Cockayne syndrome, and Rothmund-Thomson syndrome, sparse hair is evident in early infancy. A severe neonatal progeroid syndrome has been described in which severe hypotrichosis is evident at birth, along with redundant skin, absent subcutaneous fat, and prominent blood vessels.⁷²

HYPOTRICHOSIS WITH IMMUNODEFICIENCY SYNDROMES

In *cartilage hair hypoplasia syndrome*, sparsity of scalp, eyebrow, and eyelash hair is often evident in the neonatal period, together with short limbs and prenatal growth failure.⁷³ A human homologue of the *nude* mouse has recently been identified with mutations in the *winged helix nude* gene leading to complete absence of all hair and severe immunodeficiency.⁴⁹ Alopecia is also often a striking feature of a heterogeneous group of congenital immunodeficiency conditions presenting with erythroderma, failure to thrive, and diarrhea in early infancy, including *Omenn syndrome* and severe combined immunodeficiency-associated congenital graft-versus-host disease.⁷⁴



Figure 31.17 Loose anagen in a 2-year-old child, who has never had a hair-cut. The wispy ends are common in this condition. Hair mount is diagnostic. (Courtesy of Dr Ilona Frieden.)

LOOSE ANAGEN SYNDROME

Loose anagen syndrome (LAS) is a benign, self-limiting condition where anagen hairs are easily and painlessly extracted. Although this condition is not seen neonates, it may become evident in infants or toddlers because of the very sparse growth of hair with wispy ends. Because the hair pulls out easily patchy alopecia occasionally is noted (Fig. 31.17). LAS is a sporadic or autosomal dominant disorder with variable expressivity that has been linked to the genes encoding *K6HF*, the companion layer keratin and *K6IRS*, a gene specific for the internal root sheath. It can also be seen in Noonan syndrome and certain ectodermal dysplasias. A trichogram reveals a characteristic ruffling of the cuticle (Fig. 31.18) and may show misshapen anagen bulbs and long, tapered and twisted hairs. Most cases of LAS improve spontaneously with age.

Localized alopecia (Box 31.4)

TRAUMA

Alopecia in the neonatal period may occur in areas of scalp damaged by instrumentation, such as forceps, scalp monitors, and vacuum extractor, and also around a caput succedaneum (see Chapter 8). Prolonged pressure on the scalp by the cervical os during or before the delivery may result in a distinctive pattern of annular alopecia known as a halo scalp ring (Fig. 31.19).

NEONATAL OCCIPITAL ALOPECIA

A well-defined patch of alopecia commonly develops in the occipital area in the early months of life (Fig. 31.20). This has been attributed to pressure or friction due to sleeping in a supine position and/or rubbing against the bedding surface, but is explained more fully by an understanding of the patterns of hair cycle evolution in fetal and early neonatal life.⁷⁵ Although the hair roots enter catagen and then telogen in a progressive manner from frontal to parietal areas at 26–28 weeks' gestation, the roots in the occipital area remain in anagen until around

BOX 31.4 LOCALIZED ALOPECIA

- Trauma
- Neonatal occipital alopecia
- Triangular alopecia
- Tinea capitis
- Traction alopecia and trichotillomania
- Aplasia cutis congenita
- With other nevoid conditions
 - Aplastic nevus
 - Sebaceous nevus
 - Nevus psiloliparus
 - Congenital melanocytic nevus
- Meningocele, encephalocele, heterotopic meningeal and brain tissue
- Membranous aplasia cutis
- Alopecia areata
- Localized alopecia as part of syndromes
 - Hallermann–Streiff syndrome
 - X-linked dominant conditions



Figure 31.19 Halo scalp ring.



Figure 31.20 Neonatal occipital alopecia.



Figure 31.18 Ruffled cuticle and misshapen bulb in loose anagen syndrome. Light microscopic appearance.

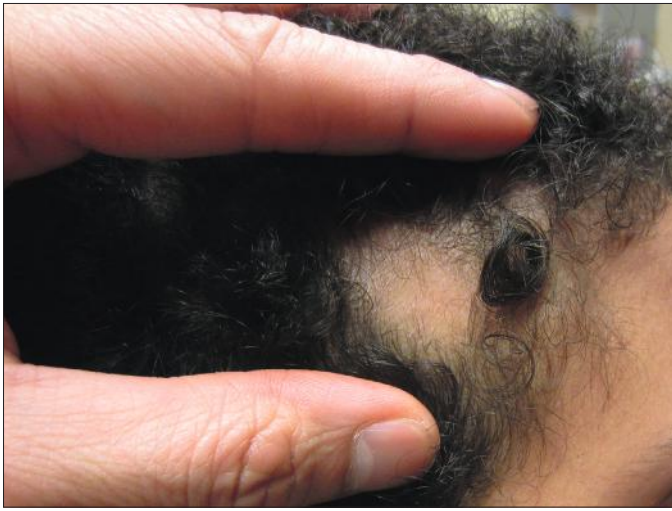


Figure 31.21 Temporal triangular alopecia.

the time of birth, when they abruptly enter telogen. These hairs inevitably fall 8–12 weeks later. Thus neonatal occipital alopecia is really a form of localized telogen effluvium. Often, there are considerable numbers of hairs in the parietal area still in telogen at birth, and a more extensive postnatal alopecia can occur, leaving hair only on the vertex. In pigmented races, there is a delay in onset of these physiologic changes as most roots are still in anagen at birth, and the mean diameter of the hairs is greater than in fair-complexioned neonates. For these reasons, the hair is often prolific at a time when the fair neonates are developing significant alopecia.

TRIANGULAR ALOPECIA

This noncicatricial circumscribed area of hypotrichosis is triangular or lance-shaped and is positioned in the frontotemporal area, with the base facing the temporal edge of the hairline but sometimes separated from it by a small fringe of normal hair (Fig. 31.21).⁷⁶ It is unilateral in 80% of cases. It is a hypotrichosis rather than a true alopecia because vellus hairs are present in the affected area. Occasionally a few terminal hairs are retained. Although the condition usually occurs sporadically it may very rarely affect several members of a family, and Happle⁷⁷ has suggested it may be a parадominant trait; he notes that it has occurred in association with phakomatosis pigmentovascularis, providing further evidence that it may result from loss of heterozygosity.⁷⁷ Histopathologic examination of transverse sections of a biopsy specimen demonstrates that the majority of follicles are vellus; a normal number of follicles are present, but their size is abnormal for the scalp.⁷⁶ The condition certainly may be congenital and may be noted in the neonatal period in infants with abundant scalp hair, in whom it is often erroneously ascribed to forceps trauma. Whether it is always congenital is disputed.⁷⁶

TINEA CAPITIS

Although rare, tinea capitis (see Chapter 14) can occur in neonates and more commonly in infants and can cause localized scaling and alopecia (Fig. 31.22). At times, it may present as a purulent scalp lesion.⁷⁸ As in older children, systemic antifungals are necessary to achieve cure.



Figure 31.23 Aplasia cutis congenita.

TRACTION ALOPECIA AND TRICHOTILLOMANIA

In the African-American population, hair-braiding practices, particularly ‘cornrows’, may predispose to traction alopecia in young children.⁷⁹ Occasionally, trichotillomania is seen in infancy.⁸⁰ Trichotillomania in early childhood is generally considered a benign habit disorder however even at a very early age, it can be an early sign of obsessive compulsive or other behavioral tendencies.

APLASIA CUTIS CONGENITA

Aplasia cutis congenita (ACC) is a congenital defect of the skin characterized by localized absence of the epidermis, dermis and, at times, underlying tissue (Fig. 31.23). Most cases are sporadic and isolated, although it may be associated with teratogenic, local or systemic anomalies (see below).⁸¹

LOCALIZED ALOPECIA ASSOCIATED WITH OTHER NEVOID CONDITIONS

Aplastic nevus (minus nevus)

This is a nevoid condition in which there is a complete absence of skin appendages in an area of otherwise normal skin.⁸²

Nevus sebaceus

Nevus sebaceus are characteristically hairless. Occasionally the affected area is so flat and subtle that it is only recognized later, such that the initial presentation is as a patch of congenital alopecia (Fig. 31.24). Large sebaceous nevus can be associated with eye and neurological impairment in nevus sebaceus syndrome. Rarely, it can be seen in conjunction with aplasia cutis congenita and other multiple anomalies in SCALP syndrome.⁸³

Nevus psiloliparus

The name nevus psiloliparus is derived from the Greek words *psilos* for hairless and *liparos* for fatty, describing the smooth-surfaced, soft, hairless lesion seen on the scalp. It can present in isolation (Fig. 31.25) or in encephalocraniocutaneous lipomatosis.⁸⁴



Figure 31.22 Tinea capitis in a 14-month-old infant caused by *Trichophyton mentagrophytes*.



Figure 31.24 Nevus sebaceus.



Figure 31.25 Nevus psiloliparus.

Congenital melanocytic nevus

These lesions (see also [Chapter 24](#)) are usually associated with hypertrichosis, but large, folded lesions on the scalp causing an appearance of cutis verticis gyrata may have sparse covering hair ([Fig. 31.26](#)).

Cranial meningoceles, encephaloceles and heterotopic meningeal or brain tissue

These (see also [Chapter 9](#)) present characteristically as tumors or cysts that are either hairless or have sparse overlying hair. There is often a surrounding collar of long hair. Membranous aplasia cutis, which is in the same spectrum, representing a forme fruste of neural tube defect, presents as a hairless plaque, sometimes also with a collar of longer hair (see below).

ALOPECIA AREATA

This condition is uncommon in infancy, and rarely occurs at birth.⁸⁵ The alopecia can be localized or generalized ([Figs 31.27, 31.28](#)). The diagnosis is made clinically, supported by a positive pull-test, exclamation point hairs, and spontaneous regrowth. The characteristic lymphocytic infiltrate around the hair bulb on cutaneous histopathology can confirm the diagnosis. Patients with an earlier age of onset tend to have a greater severity of disease, in terms of extent of alopecia and chance of regrowth,⁸⁶



Figure 31.27 Alopecia areata. (Courtesy of Dr Ilona Frieden.)

although early age of onset does not rule out future hair regrowth.⁸⁷ Therapies for alopecia areata in this age group include topical corticosteroids, topical minoxidil, and most importantly patient and family support.⁸⁵

LOCALIZED ALOPECIA ASSOCIATED WITH SYNDROMES

Hallermann–Streiff syndrome

The hair may be normal at birth, but in some cases the typical alopecia, located in the frontal and parietal areas over the cranial sutures, may be evident in early months together with atrophic facial skin and multiple craniofacial and ocular abnormalities.⁸⁸

X-linked dominant conditions

Several rare syndromes caused by X-linked dominant genes that interfere with hair growth produce a mosaic pattern of alopecia in affected females as a result of functional X-chromosome mosaicism.⁸⁹ The hemizygous males with these conditions rarely survive. The conditions include incontinentia pigmenti, focal dermal hypoplasia (Goltz syndrome), X-linked dominant chondrodysplasia punctata, orofacial digital syndrome, and CHILD syndrome. The alopecia in these conditions has a patchy distribution, sometimes obviously linear or spiral as it follows the lines of Blaschko.⁸⁹

Diffuse hypertrichosis

The term ‘hypertrichosis’ refers to increased hair, whereas hirsutism refers specifically to increased hair in hormonally responsive areas of skin (such as the axillae, pubic area, and beard area). Hirsutism in neonates and young infants is rare and is virtually always a result of congenital endocrine disorders. Hypertrichosis, on the other hand, can result from a wide variety of conditions.

PRIMARY HYPERTRICHOSIS

There is much confusion about congenital hypertrichosis occurring alone or with only occasional associations, because



Figure 31.26 Congenital melanocytic nevus with grossly folded scalp and alopecia. (Courtesy of Dr Marcelo Ruvertori.)



Figure 31.28 Alopecia areata in an 18-month-old girl.

BOX 31.5 DIFFUSE HYPERTRICHOSIS

- Primary hypertrichosis
- Transient diffuse hypertrichosis
- Hypertrichosis lanuginosa
- Prepubertal hypertrichosis
- X-linked hypertrichosis
- Ambras syndrome
- Hypertrichosis as part of other genetically determined disorders
 - Hypertrichosis with gingival fibromatosis
 - Hypertrichosis with osteochondrodysplasia
 - Hypertrichosis, pigmentary retinopathy and facial anomalies
 - Hypertrichosis with cone rod dystrophy
 - Hypertrichosis with congenital cataract and mental retardation
 - Coffin–Siris syndrome
 - Cornelia de Lange syndrome
 - Leprechaunism
 - Seip–Berardinelli syndrome (congenital generalized lipodystrophy)
 - Rubinstein–Taybi syndrome
 - Barber–Say syndrome
- Drug-induced hypertrichosis
 - Fetal alcohol syndrome
 - Maternal minoxidil
- Diazoxide

of the wide variety of designations given and the poor clinical descriptions in the early literature. Baumeister and colleagues,⁹⁰ and more recently, Garcia-Cruz and coworkers,⁹¹ have attempted to clarify the classification, but some confusion persists. However, several apparently individual entities can be separated out (Box 31.5).

TRANSIENT DIFFUSE HYPERTRICHOSIS

Lanugo is the fine unmedullated hair that is present in the fetus. The hairs are several centimeters long and usually nonpigmented.⁹² Growth occurs on the entire body, including the face. This hair is normally shed at around 7–8 months' gestation. However, in some neonates, especially if premature, diffuse lanugo hair is still present and is most marked on the shoulders, posterior trunk, cheeks and sometimes ears (Fig. 31.29). This is then shed in the early weeks of life.

HYPERTRICHOSIS LANUGINOSA

This rare condition is characterized by prolonged retention of lanugo hair. The infant is born with a coat of profuse, long, silky, fine, hair on all the usual hair-bearing areas.⁹³ It may reach 10 cm in length and blends with the terminal hair of scalp and eyebrows (Fig. 31.30). There may be accentuation in certain areas, particularly over the spine and on the pinnae. Profuse growth in the ear canal may lead to infection and reduced hearing, and needs to be cleared. Matted hair in the diaper area is particularly troublesome, and shaving or laser hair removal in this and other areas may be indicated. A 40–80% reduction in hair has been noted in laser-treated areas using low fluences to minimize pain.^{94–96} At puberty, there may be no conversion to terminal hair in secondary sexual hair areas, with long, fine, lanugo hairs growing in the beard, pubic, and axillary areas. Although about one-third of cases are sporadic, autosomal



Figure 31.29 (A) Transient neonatal hypertrichosis with marked involvement of the helix and adjacent skin. (B) A 2-week-old infant with diffuse lanugo hair on the back. (C) At age 4 months, this hair is no longer present.

dominant inheritance is well established.^{91,93} However, a single family with possible autosomal recessive inheritance has also been reported. Most patients are free of other abnormalities, but congenital glaucoma, skeletal,⁹⁷ and dental⁹⁴ abnormalities, including neonatal teeth, have been observed.



Figure 31.30 Hypertrichosis lanuginosa.

PREPUBERTAL HYPERTRICHOSIS

A series has been reported⁹⁸ of otherwise healthy children, with no clinical evidence of endocrinopathy, having generalized hypertrichosis present from birth and increasing in severity in early childhood. There is terminal hair growth on the temples, spreading across the brow and merging with bushy eyebrows, and also profusely on the back and proximal limbs.⁹⁸ The pattern does not resemble hirsutism and hair growth on the back is in an inverted fir tree distribution, centering on the spine. It is not clear whether this represents an abnormality or whether it is an extreme form of the normal range of hair growth, resembling as it does the patterns of hair growth seen regularly in some racial groups.⁹⁸ However, a 2000 study has demonstrated that testosterone levels and the free androgen index are increased in patients compared to controls. This suggests that an endocrine imbalance may indeed be the basis for this condition.⁹⁹

X-LINKED DOMINANT HYPERTRICHOSIS

A pedigree has been reported with probable X-linked dominant inheritance where affected members have generalized terminal hair hypertrichosis present at birth.¹⁰⁰ The face, pubic area, back, and upper chest are most involved, but the palms, soles, and mucosae are spared. There is no gingival hyperplasia. After puberty there may be an improvement on the trunk and limbs. This condition has been mapped to a 22-cM interval between *DXS425* and *DXS1227* on chromosome Xq24-q27.1.¹⁰¹

AMBRAS SYNDROME

Baumeister and colleagues¹⁰² have delineated what they regard as a unique form of diffuse congenital hypertrichosis which has been previously reported under a variety of names, and have demonstrated a balanced structural chromosomal aberration in

a patient with this condition. It has been designated 'Ambras syndrome' in reference to the first documented case. The hair, which may demonstrate pigmentation and medullation, is said to be vellus rather than lanugo. The hypertrichosis is most marked on the face, nose, ears, and shoulders, and the forehead, eyelids, cheeks, and preauricular regions show hair of variable lengths.⁹¹ The palms, soles, mucous membranes, dorsal terminal phalanges, labia minora, prepuce, and glans penis are always spared.⁹¹ The hypertrichosis persists throughout life. A number of dysmorphic facial features (coarse face, wide intercanthal distance, broad palpebral fissures, broad interalar distance and anteverted nares) and dental abnormalities (anodontia and delayed secondary dentition) may be present.^{91,103} An autosomal dominant inheritance is proposed, with the causative gene mutation found on chromosome 8q22-q24.^{91,103}

HYPERTRICHOSIS AS PART OF OTHER GENETICALLY DETERMINED DISORDERS

Many syndromes have hypertrichosis as a feature, and in some of these it is present in the neonatal period. A selection of these conditions is considered here.

Hypertrichosis with gingival fibromatosis

Hypertrichosis and gingival fibromatosis may occur as a dominantly inherited trait and is usually caused by microdeletions on chromosome 17q24.2-q24.3.^{92,104,105} The hypertrichosis is usually of terminal hair, but may be relatively mild. It can be present at birth or develop during early infancy, but in up to half of the reported cases the hypertrichosis begins at puberty.⁹⁷ The gingival hyperplasia appears later in childhood. Other clinical features include a coarse facies with a wide, flat nose and thick lips, and large ears.⁹¹

Several patients have been reported with epilepsy and mental retardation in association with severe hypertrichosis and gingival fibromatosis.¹⁰⁶ The gingival fibromatosis in this condition usually presents in the second decade but has been reported in infancy. The hypertrichosis is congenital, and the hair varies from fine to coarse and is pigmented. The face, arms, and lumbosacral area are most severely affected. It is possible that these conditions are within a single spectrum.

Further overlap is suggested with the Laband syndrome of gingival hyperplasia, dysplasia of the terminal phalanges, hepatosplenomegaly, and facial dysmorphism, with the recent report of marked congenital hypertrichosis as an additional feature in one patient.¹⁰⁷

Hypertrichosis with osteochondrodysplasia

This rare syndrome (also known as Cantu syndrome) is the combination of diffuse congenital hypertrichosis, congenital macrosomia, cardiomegaly which may also be present at birth, and a variety of skeletal changes.⁹¹ The hair changes from lanugo to postnatal hair, which continues to grow in length and diameter, extending all over the body but sparing the palms, soles, and mucosae.⁹¹ It is most marked on the face, with involvement of the forehead and thick eyebrows, and there is a low posterior cervical hairline. Other features include mild mental retardation, macrocephaly, global cardiomegaly due to cardiomyopathy (sometimes complicated by pericarditis with effusion),⁹¹ and a variety of skeletal changes, including a wide posterior fossa in the skull, a verticalized base of the cranium, narrow thorax, broad ribs, bilateral coxa valga, a short distal

phalanx of the thumbs and first toes, and hypertrophy of the first metatarsals.⁹¹ Most cases are autosomal dominant and are caused by heterozygous mutation in the *ABCC9* gene on chromosome 12p12.¹⁰⁸

Hypertrichosis with congenital eye disorders

Hypertrichosis, pigmentary retinopathy, and facial anomalies. An apparently distinct form of congenital hypertrichosis has been reported in one male patient.¹⁰⁹ At birth, long, fine, dark hair covered the shoulders, back, buttocks, and limbs; the chest and abdomen were relatively spared. A biopsy from an arm showed a smooth muscle proliferation suggestive of smooth muscle hamartoma. Associated findings were pigmentary retinopathy and dysmorphic facial features. The finding of hypopigmented and hyperpigmented streaks following Blaschko's lines on the limbs suggested mosaicism, but this could not be confirmed on chromosomal studies of lymphocytes and skin fibroblasts.¹⁰⁹

Hypertrichosis with cone/rod dystrophy. In 1999, Jalili¹¹⁰ reported two female cousins with Leber's amaurosis, with cone/rod dystrophy and congenital hypertrichosis.⁹¹ They had severe retinal dystrophy with visual impairment from birth and profound photophobia in the absence of night blindness. Trichomegaly, bushy eyebrows with synophrys, and excessive facial and body hair, including hypertrophied circumareolar hair on the breast, were present. An autosomal recessive inheritance pattern was proposed.¹¹⁰

Hypertrichosis with congenital cataracts and mental retardation. A new autosomal recessive syndrome characterized by congenital lamellar cataracts, generalized hypertrichosis on the back, shoulders, and face, and mental retardation (CAHMR syndrome) was reported in 1992.¹¹¹ Associated findings were a low hairline, high narrow palate, macrodontia, and pectus excavatum.¹¹¹

Coffin–Siris syndrome

Hypertrichosis is a feature in many cases,¹¹² particularly of the face and back; there is a low frontal hairline, bushy laterally displaced eyebrows, and long eyelashes, but often sparse scalp hair. Also evident in the neonatal period are absence or hypoplasia of the nails and distal phalanges of the fifth fingers and toes, microcephaly, facial dysmorphism, and low birthweight. Short stature is common, as is delayed bone age. Spinal anomalies are also frequently seen, including sacral dimples, spina bifida occulta, scoliosis, and kyphosis. Mental retardation becomes evident later. The region 7q32–34 is a candidate region for the gene responsible for this syndrome.¹¹³

Cornelia de Lange syndrome

There is a mild generalized hypertrichosis with low frontal and occipital hairlines, thick eyebrows, synophrys, and long, upturned lashes (Fig. 31.31). The hair on the lateral elbows and sacral area may be very long and fine. Other features notable in the neonatal period include congenital livedo, low birthweight, feeding difficulties, increased susceptibility to infection, and an unusual low-pitched growling cry. There is a distinctive facies with hypertelorism, an antimongoloid slant of the palpebral fissures, long philtrum, and thin lips. Other features in occasional cases include micromelia and phocomelia, cryptorchidism, and hypospadias.



Figure 31.31 Cornelia de Lange syndrome.

Leprechaunism (Donohue syndrome)

These infants have coarse, curly scalp hair, and 75% of cases have extensive body and facial hypertrichosis.¹¹⁴ There is low birthweight, wrinkled loose skin with reduced or absent subcutaneous fat, acanthosis nigricans, periorificial rugosity of skin, thick lips, gingival hypertrophy, large low-set ears, and hypertrophic external genitalia.

Seip–Berardinelli syndrome (congenital generalized lipodystrophy)

Hypertrichosis of the face, neck, and limbs may be present at birth. There is thick, curly scalp hair with a low frontal hairline. Other features that may be evident in the neonatal period include deficiency of subcutaneous fat, acanthosis nigricans, organomegaly, and hypertrophy of genitalia.

Rubinstein–Taybi syndrome

In Rubinstein–Taybi syndrome, hypertrichosis of the trunk, limbs, and face occurs in two-thirds of cases.¹¹⁵ The eyebrows are highly arched and the eyelashes unusually long. There are downward-sloping palpebral fissures and mental retardation. Other features evident in the neonatal period include capillary vascular malformations, pilomatricomas, keloid formation, beaked nose, hypertelorism, cryptorchidism, broad thumbs and great toes, and sometimes broad terminal phalanges of the other digits. This syndrome is sporadic in nature and has been linked to a deletion in the *CREBBP* and *EP300* genes.¹¹⁶

Barber–Say syndrome

In this rare syndrome, extensive generalized hypertrichosis, most marked over the forehead and back, is associated with redundant atrophic skin showing changes of premature aging, coarse face with bilateral ectropion, hypertelorism, absent eyebrows and lashes, bulbous nose with anteverted nares, macrostomia, abnormal ears, ectropion, hypoplastic nipples, and

failure to thrive.^{91,117} Other features, less frequently reported, include strabismus, nystagmus, mental retardation, small teeth, and high arched palate.⁹¹

DRUG-INDUCED NEONATAL HYPERTRICHOSIS

Fetal alcohol syndrome

Neonatal hypertrichosis is an occasional feature of this condition.¹¹⁸ The infant is small and microcephalic with dysmorphic facial features, including short palpebral fissures, microphthalmia, midfacial hypoplasia, and a long philtrum.

Maternal minoxidil

Maternal use of minoxidil during pregnancy has been associated with a striking hypertrichosis of the back and extremities in the neonate, accompanied by multiple dysmorphic facial features, uneven fat distribution, omphalocele, and cardiac anomalies.¹¹⁹

Diazoxide

Diazoxide is commenced in babies with hyperinsulinemia as soon as the diagnosis is established, usually in the first week of life; hypertrichosis of brow, limbs, and back becomes obvious in the first 4 weeks of treatment and is dose dependent.

Localized congenital hypertrichosis

Localized hypertrichosis may occur in association with certain nevi or developmental abnormalities (Box 31.6).

CONGENITAL MELANOCYTIC NEVUS

Congenital melanocytic nevi may be covered with dense, dark terminal hair at birth over part or all of their surface (Fig. 31.32). In areas other than the scalp, the degree of hairiness is usually proportional to the degree of elevation of the lesion. On the scalp, however, even very flat lesions often have a dense covering of hair that is longer, darker, and coarser than the surrounding scalp hair.

CONGENITAL SMOOTH MUSCLE HAMARTOMA

These nevi present most commonly as congenital, slightly elevated, pebbly, firm skin-colored or slightly pigmented plaques,

with local hypertrichosis (Fig. 31.33).¹²⁰ Most occur on the trunk or the proximal extremities, but other areas, including the scalp,¹²¹ may be affected. A pseudo-Darier sign of transient piloerection or elevation of the lesion after it is rubbed is a characteristic feature. Extensive hypertrichosis overlying diffuse, widespread, smooth muscle hamartomas has also been reported.¹²² Histopathologic examination demonstrates a proliferation of variably oriented smooth muscle bundles, often associated with hair follicles. There may also be epidermal changes of acanthosis and papillomatosis, as seen in Becker nevus.

Becker nevus usually presents in late childhood or adolescence as a patch of thickened, pigmented, hypertrichotic skin. Congenital cases have been reported, although usually lacking hypertrichosis in the neonatal period.¹²³ These nevi are uncommon in females.¹²⁰ An unusual presentation with congenital bilaterally symmetric lesions, hypertrichotic at birth, has been reported.¹²⁴ Some believe that congenital smooth muscle hamartoma and Becker nevus are in a spectrum,¹²⁵ but others feel they are distinct entities.¹²⁶



Figure 31.32 Long, dark hair on congenital melanocytic nevus of scalp.



Figure 31.33 Congenital smooth muscle hamartoma.

BOX 31.6 LOCALIZED HYPERTRICHOSIS

- Congenital melanocytic nevus
- Congenital smooth muscle hamartoma
- Hypertrichosis over plexiform neurofibroma
- Tufted angioma
- Hypertrichosis with spinal fusion abnormalities
- Familial cervical hypertrichosis with kyphoscoliosis
- Associated with cranial meningoceles, encephaloceles, and heterotopic meningeal or brain tissue
- Nevoid hypertrichosis
- Hemihypertrophy with hypertrichosis
- Scrotal hair
- Anterior cervical hypertrichosis
- Hairy cutaneous malformations of palms and soles
- Hypertrichosis cubiti
- Ectopic cilia
- Distichiasis
- Hypertrichosis pinnae auris

PLEXIFORM NEUROFIBROMA

The skin over these lesions is often notable for a patch of hyperpigmentation with an irregular border and hypertrichosis of varying degree.¹²⁷ A prominent paraspinal hair whorl may also occur at the site of a deep mediastinal plexiform neurofibroma.¹²⁸ A similar paraspinal whorl has been described in a patient with a posterior mediastinal ganglioneuroma.¹²⁹ Erythema may also be a feature, leading to confusion with vascular tumors such as tufted angiomas and kaposiform hemangioendotheliomas, that may themselves have associated focal hypertrichosis.

TUFTED ANGIOMA

This is a rare benign vascular tumor found particularly on the neck and upper trunk regions, as well as the abdomen, groin, and lower limbs. Most commonly they present as dusky red to violaceous, indurated, subcutaneous plaques or nodules; 30% of lesions are tender.¹³⁰ Some have been associated with focal hyperhidrosis and/or hypertrichosis.¹³¹

HYPERTRICHOSIS WITH SPINAL DYSRAPHISM

Isolated hypertrichosis in the lumbosacral region may be a normal variant and is usually genetically or racially determined. It should be distinguished from hypertrichosis associated with an underlying spinal abnormality. This latter presents at birth as a tuft of long, silky hair (faun tail) with or without the presence of other cutaneous markers, such as a dimple, sinus tract, aplasia cutis, lipoma with deviation of the gluteal fold, capillary malformation, hemangioma, or a pigmented nevus.^{132–134} These cutaneous lesions may be found in the presence of clinical spina bifida with myelomeningocele (Fig. 31.34), but are particularly helpful as markers for occult spinal dysraphism. Two or more congenital midline skin lesions constitute a particularly strong marker for spinal dysraphism.¹³⁴ Hypertrichosis associated with spinal fusion abnormalities may also occur less commonly over other areas of the spine.

FAMILIAL CERVICAL HYPERTRICHOSIS DYSRAPHISM

A family has been reported with congenital localized hypertrichosis of the cervical area overlying a kyphoscoliosis without other spinal or cutaneous abnormalities.¹³⁵ The inheritance pattern was autosomal dominant.

HYPERTRICHOSIS WITH CRANIAL MENINGOCELES, ENCEPHALOCELES, AND HETEROTOPIC MENINGEAL OR BRAIN TISSUE

These conditions are described in detail in Chapter 9. They are often marked by a peripheral collar of hair (Fig. 31.35), a tuft of hair nearby, or overlying hair.¹³³ In scalp lesions the hair is longer, thicker, and often darker than the surrounding normal hair. An associated vascular stain may also be present.¹³⁶ With lesions outwith the scalp, the presence of hair may indicate a neural lesion (Figs 31.36, 31.37). Prominent hair follicle orifices may also be a feature. It is now clear that the membranous form of aplasia cutis, which may also demonstrate a hair collar and



Figure 31.35 Heterotopic brain tissue on scalp with hair collar.



Figure 31.37 Heterotopic brain tissue on the cheek with prominent hair follicle orifices and superimposed hypertrichosis.

which can occur on the face^{133,137,138} as well as the scalp, is a form fruste of a neural tube closure defect and in the same spectrum as cranial meningoceles, encephaloceles, and heterotopic brain tissue.¹³³ A patient has been reported with a congenital patch of hypertrichosis over the lumbar area, well away from the spine, overlying what was demonstrated histologically to be meningeal tissue; in this case, displacement of meningeal cells along nerves during embryogenesis is postulated as the mechanism, rather than entrapment of meningeal membranes at the time of closure of the neural tube.¹³⁹

NEVOID HYPERTRICHOSIS

Several patients have been reported with single or multiple localized patches of terminal hair arising in skin which is otherwise normal in color and texture (Fig. 31.38).^{120,140,141} Presentation is usually at or soon after birth, although the development of additional patches after puberty has been described. The color of the hair is typically the same as that of the scalp, but rarely the hair may be paler or there may be premature graying.



Figure 31.34 Faun tail nevus (tuft of long fine hair) in association with spina bifida with myelomeningocele.

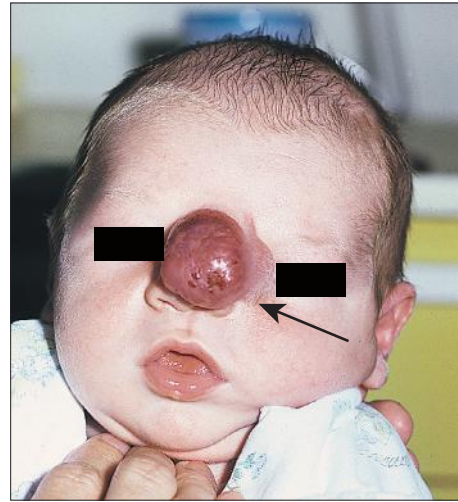


Figure 31.36 Encephalocele with surrounding hypertrichosis (arrow).



Figure 31.38 Area of nevoid hypertrichosis.

In one case, underlying lipoatrophy was found in some patches.¹⁴⁰ Additional abnormalities seen in another patient included areas of lipoatrophy and streaky depigmentation away from the areas of hypertrichosis, developmental delay and seizures, congenital lung cysts, congenital malrotation of the gut, and multiple skeletal, dental, and ocular abnormalities.¹⁴¹ This constellation of findings did not fit into any recognized syndrome. The excess hair can be treated with laser.¹⁴²

There have also been a few cases of hypertrichosis overlying lesions of nevus spilus.¹⁴²

HEMIHYPERTROPHY WITH HYPERTRICHOSIS

Hemihypertrophy is a rare congenital disorder in which the whole of one side of the body or, less commonly, part of one side of the body is enlarged. Serious associated malformations include Wilms tumor and tumors of the brain and adrenals. The skin is often normal, but cutaneous abnormalities reported include pigmentation, telangiectasia, abnormal nail growth, and hypertrichosis, which can be very striking.¹⁴³

SCROTAL HAIR

Several infant boys have been reported who developed scrotal hair within the first 3 months of life in the absence of clinical or biochemical evidence of excess androgen production (Fig. 31.39).¹⁴⁴ The condition is not progressive and most cases are sporadic. It is most likely caused by an increased hypersensitivity of scrotal hair follicles in affected infants to the normal 'physiological' high concentrations of testosterone seen in early infancy.¹⁴⁴ As concentrations decrease later in infancy, the scrotal hair disappears or diminishes. Although this is a benign condition, it should be regarded only as a diagnosis of exclusion and all infants with signs suggestive of androgenization should be fully investigated.

ANTERIOR CERVICAL HYPERTRICHOSIS

A congenital patch of hypertrichosis localized to the front of the neck at the sternal notch has been described and the inheritance pattern is most likely autosomal recessive.^{91,145} Although usually an isolated finding, it may be associated with peripheral sensory and motor neuropathy,¹⁴⁶ retinal abnormalities, developmental delay and learning difficulties.¹⁴⁷



Figure 31.41 (A,B) Hypertrichosis over the outer pinna in a 2-month-old infant. (Courtesy of Dr Ilona Frieden.)

HAIRY CUTANEOUS MALFORMATIONS OF PALMS AND SOLES

There have been reports of the familial occurrence of hair growth on circumscribed areas of the palms and soles.¹⁴⁸ In one family, the skin in the area showed exaggerated markings in a geometric pattern. The condition was present at birth and persisted throughout life. Histopathology demonstrated the presence of ectopic hair follicles and some increase in the amount of elastic fibers in the dermis.

HYPERTRICHOSIS CUBITI

In 'hairy elbows syndrome' lanugo hairs are present symmetrically at birth or develop during infancy on the extensor surfaces of the elbows, extending from midhumerus to midforearm.^{97,149} This syndrome is not usually associated with other anomalies and most frequently only represents a cosmetic problem. There

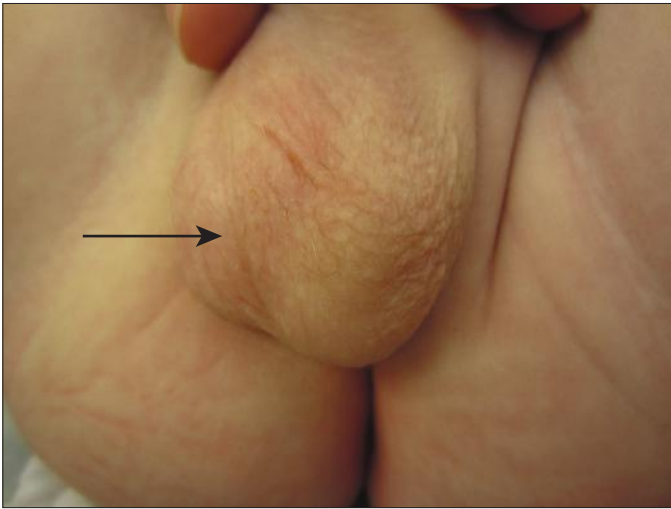


Figure 31.39 Idiopathic scrotal hair (arrow).



Figure 31.40 Ectopic cilia. (Courtesy of Dr Amy Gilliam.)

have, however, been isolated case reports of hypertrichosis cubiti associated with short stature.¹⁴⁹

ECTOPIC CILIA

The eyelashes or cilia are modified hairs originating from follicles on the margins of the eyelids. The rarest of all cilial anomalies is ectopic placement. The locations of the ectopic cilia fall into two distinct groups: those originating anterior to the tarsal plate and those arising from the posterior surface of the tarsus. Ectopic cilia arising anterior to the tarsal plate are all seen within the lateral quarter of the lid, with multiple hairs (15–20) surrounding a pit, and the bulbs of the follicles being tightly adherent to the underlying tarsus (Fig. 31.40). Ectopic cilia originating from the posterior surface of the tarsal plate presents with a single lash seen beneath the conjunctiva; the position on the lid varies. The two forms of lesion have different etiologic origins.¹⁵⁰

DISTICHIASIS

This term refers to lashes arising from the Meibomian gland orifices. This can occur as a result of eyelid inflammation, but

there is an inherited congenital form in which there is a double row of lashes, the normal row and a row arising from meibomian gland orifices. This condition can be inherited alone or more commonly as part of lymphedema–distichiasis syndrome. Mutations in the *FOXC2* gene have been identified in both groups, suggesting they are phenotypic varieties of the same disorder.¹⁵¹

HYPERTRICHOSIS PINNAE AURIS

Hypertrichosis pinnae auris, also known as ‘hairy ears’ describes the development of hairs on the outside of the pinna of the ear (Fig. 31.41). It is a benign finding seen in many ethnic groups and usually resolves with time. It may be caused by sex-limited expression of an autosomal dominant gene.¹⁵²

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Figures 2, 3, 5, 6, 8, 12, 18, 22, 26, 28, 34, 36, 39 and 40 are available online at [ExpertConsult.com](https://www.expertconsult.com)

KEY REFERENCES

3. Furdon SA, Clark DA. Scalp hair characteristics in the newborn infant. *Adv Neonatal Care* 2003;3:286–96.
47. Sprecher E. Genetic hair and nail disorders. *Clin Dermatol* 2005;23:47–55.
58. Itin PH, Fistarol SK. Ectodermal dysplasias. *Am J Med Genet* 2004;131C:45–51.
81. Frieden I. Aplasia cutis congenita: a clinical review and proposal for classification. *J Am Acad Dermatol* 1986;14(4):646–60.
91. Garcia-Cruz D, Figueroa LE, Cantu JM. Inherited hypertrichoses. *Clin Genet* 2002;61:321–9.
97. Vashi R, Mancini A, Paller A. Primary generalized and localized hypertrichosis in children. *Arch Dermatol* 2001;137:877–84.
133. Drolet B. Cutaneous signs of neural tube malformations. *Semin Cutan Med Surg* 2004;23:125–37.

REFERENCES

- Pecoraro V, Astore I, Barman JM. Cycle of the scalp hair of the newborn child. *J Invest Dermatol* 1964;43:145–7.
- Barman JM, Pecoraro V, Astore I, et al. The first stage in the natural history of the human scalp hair cycle. *J Invest Dermatol* 1967;48:138–42.
- Furdon SA, Clark DA. Scalp hair characteristics in the newborn infant. *Adv Neonatal Care* 2003;3:286–96.
- Smith DW, Gong BT. Scalp hair patterning as a clue to early fetal brain development. *J Pediatr* 1973;83:374–80.
- Wunderlich RC, Heerema NA. Hair crown patterns of human newborns. *Clin Pediatr* 1975;14:1045–9.
- Tirosh E, Jaffe M, Dar H. The clinical significance of multiple hair whorls and their association with unusual dermatoglyphics and dysmorphic features in mentally retarded Israeli children. *Eur J Pediatr* 1987;146:568–70.
- Klar AJ. Human handedness and scalp hair-whorl direction develop from a common mechanism. *Genetics* 2003;165:269–76.
- Lee WS, Lee IW, Ahn SK. Diffuse heterochromia of scalp hair. *J Am Acad Dermatol* 1996;35:823–5.
- Iorizzo M, Piraccini BM, Tosti A. Heterochromia of the scalp hair following Blaschko lines. *Pediatr Dermatol* 2007;24:69–70.
- Whiting D. Structural abnormalities of the hair shaft. *J Am Acad Dermatol* 1987;16:1–25.
- Price VH. Structural abnormalities of the hair shaft. In: Orfanos C, Happle R, editors. *Hair and hair diseases*. Berlin: Springer Verlag; 1990. p. 363–422.
- Rogers M. Hair shaft abnormalities: Part I. *Aust J Dermatol* 1995;36:179–86.
- Rogers M. Hair shaft abnormalities: Part II. *Aust J Dermatol* 1996;37:1–11.
- Rudnicka L, Olszewska M, Rakowska A, et al. Trichoscopy update 2011. *J Dermatol Case Rep* 2011;5:82–8.
- Djabali K, Panteleyev AA, Lalin T, et al. Recurrent missense mutations in the hair keratin gene hHb6 in monilethrix. *Clin Exp Dermatol* 2003;28:206–10.
- Zlotogorski A, Marek D, Horev L, et al. An autosomal recessive form of monilethrix is caused by mutations in DSG4: clinical overlap with localized autosomal recessive hypotrichosis. *J Invest Derm* 2006;126:1292–6.
- Chelly J, Tumer Z, Tonnesen T, et al. Isolation of a candidate gene for Menkes disease that encodes a potential heavy metal binding protein. *Nature Genet* 1993;3:14–19.
- Goetyn M, Geerts M-L, Kint A, et al. The Bazex-Dupre-Christol syndrome. *Arch Dermatol* 1994;130:337–42.
- Selvaag E. Pili torti and sensorineural hearing loss. A follow-up of Bjornstad's original patients and a review of the literature. *Eur J Dermatol* 2000;10:91–7.
- Silengo M, Valenzise M, Spada M, et al. Hair anomalies as a sign of mitochondrial disease. *Eur J Pediatr* 2003;162:459–61.
- Hartley J, Zachos N, Dawood B, et al. Mutations in TTC37 cause trichohepatoenteric syndrome (phenotypic diarrhea of infancy). *Gastroenterology* 2010;138:2388–98.
- Itin PH, Sarasin A, Pittelkow MR. Trichothiodystrophy: Update on the sulfur deficient brittle hair syndromes. *J Am Acad Dermatol* 2001;44:891–920.
- Nakabayashi K, Amann D, Ren Y, et al. Identification of C7orf11 (TTDN1) gene mutations and genetic heterogeneity of non-photosensitive trichothiodystrophy. *Am J Med Genet* 2005;76:510–16.
- Taylor EM, Broughton BC, Botta E, et al. Xeroderma pigmentosum and trichothiodystrophy are associated with different mutations in the XPD(ERCC2) repair/transcription gene. *Proc Natl Acad Sci USA* 1997;94:8658–63.
- Weeda G, Eveno E, Donker I, et al. A mutation in the XPD/ERCC3 DNA repair transcription gene, associated with trichothiodystrophy. *Am J Hum Genet* 1997;60:320–9.
- Nishiwaki Y, Kobayashi N, Imoto K, et al. Trichothiodystrophy fibroblasts are deficient in the repair of ultraviolet-induced cyclobutane pyrimidine dimers and (6–4) photoproducts. *J Invest Dermatol* 2004;122:526–32.
- Petrin JH, Meckler KA, Sybert VP. A new variant of trichothiodystrophy with recurrent infections, failure to thrive and death. *Pediatr Dermatol* 1998;15:31–4.
- Tolmie JL, de Berker D, Dawber R, et al. Syndromes associated with trichothiodystrophy. *Clin Dysmorphol* 1994;3:1–14.
- Brusasco A. The typical 'tiger-tail' pattern of the hair shaft in trichothiodystrophy may not be evident at birth. *Arch Dermatol* 1997;133:249.
- Khan S, Habib R, Mir H, et al. Mutations in the LPAR6 and LIPH genes underlie autosomal recessive hypotrichosis/woolly hair in 17 consanguineous families from Pakistan. *Clin Exp Dermatol* 2011;36:652–4.
- Taylor A. Hereditary woolly hair with ocular involvement. *Br J Dermatol* 1990;123:523–6.
- Neild VS, Pegum JS, Wells RS. The association of keratosis pilaris atrophicans and woolly hair, with or without Noonan's syndrome. *Br J Dermatol* 1984;110:357–62.
- Ouvrier RA. Giant axonal neuropathy. *Brain Dev* 1989;11:207–14.
- McCoy G, Protonotarios N, Crosby A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). *Lancet* 2000;42:319–27.
- Cheong JE, Wessagowit V, McGrath JA. Molecular abnormalities of the desmosomal protein desmoplakin in human disease. *Clin Exp Dermatol* 2005;30:261–6.
- Whitlock NV, Wan H, Morley SM, et al. Compound heterozygosity for non-sense and missense mutations in desmoplakin underlies skin fragility/woolly hair syndrome. *J Invest Dermatol* 2002;118:232–8.
- Hicks J, Metry DW, Barrish J, et al. Uncombable hair (cheveux incoiffables, pili trianguli et canalliculi) syndrome: Brief review and role of scanning electron microscopy in diagnosis. *Ultrastruct Pathol* 2001;25:99–103.
- Marren P, Wilson C, Dawber RPR, et al. Hereditary hypotrichosis (Marie-Unna type) and juvenile macular degeneration. *Clin Exp Dermatol* 1992;17:189–91.
- Camacho F, Ferrando J, Pichardo AR, et al. Rapp-Hodgkin syndrome with pili canalliculi. *Pediatr Dermatol* 1993;10:54–7.
- Micali GM, Cook B, Blekys I, et al. Structural hair abnormalities in ectodermal dysplasia. *Pediatr Dermatol* 1990;7:27–32.
- Giehl KA, Ferguson DJ, Dawber RP, et al. Update on detection, morphology and fragility in pili annulati in three kindreds. *J Eur Acad Dermatol Venereol* 2004;18:654–8.
- Giehl KA, Rogers MA, Radivojkov M, et al. Pili Annulati: refinement of the locus on chromosome 12q24.33 to a 2.9-Mb interval and candidate gene analysis. *Br J Dermatol* 2009;160(3):527–33.
- Ong C, O'Toole EA, Ghali L, et al. LEKTI demonstrable by immunohistochemistry of the skin: a potential diagnostic test for Netherton syndrome. *Br J Dermatol* 2004;151:1253–7.
- Menne T, Weisman K. Canestick lesions of vellus hair in Netherton's syndrome. *Arch Dermatol* 1985;121:451.
- Lurie R, Ben-Zion G. Helical hairs: A new hair anomaly in a patient with Netherton's syndrome. *Cutis* 1995;55:349–52.
- Baden HP, Kubilus J. Analysis of hair from alopecia congenita. *J Am Acad Dermatol* 1980;3:623–6.
- Sprecher E. Genetic hair and nail disorders. *Clin Dermatol* 2005;23:47–55.
- Van Steensel MA, van Geel M, Steiljen PM. Molecular genetics of hereditary hair and nail disease. *Am J Med Genet* 2004;131C:52–60.
- Irvine AD, Christiano AM. Hair on a gene string: recent advances in understanding the molecular genetics of hair loss. *Clin Exp Dermatol* 2001;26:59–71.
- Roberts JL, Whiting DA, Henry D. Marie Unna congenital hypotrichosis: Clinical description, histopathology, scanning electron microscopy of a previously unreported large pedigree. *J Invest Dermatol* 1999;4:261–7.
- Wen Y, Liu Y, Xu Y, et al. Loss-of-function mutations of an inhibitory upstream ORF in the human hairless transcript cause Marie Unna hereditary hypotrichosis. *Nature Genet* 2009;41:228–33.
- Mansur A, Elcioglu N, Redler S, et al. A Marie Unna hereditary hypotrichosis: a Turkish family with loss of eyebrows and a U2HR mutation. *Am J Med Genet* 2010;152A:2628–33.
- Zlotogorski A, Panteleyev AA, Aita VM, et al. Clinical and molecular diagnostic criteria of congenital atrichia with papular lesions. *J Invest Dermatol* 2001;117:1662–5.
- Miller J, Djabali K, Chen T, et al. Atrichia caused by mutations in the vitamin D receptor gene is a phenocopy of generalized atrichia caused by mutations in the hairless gene. *J Invest Derm* 2001;117:612–17.
- Rapelanoro R, Taieb A, Lacombe D. Congenital hypotrichosis and milia: Report of a large family suggesting X-linked dominant inheritance. *Am J Med Genet* 1994;52:487–90.
- Indelman M, Leibur R, Jammal A, et al. Molecular basis of hypotrichosis with juvenile macular dystrophy in two siblings. *Br J Dermatol* 2005;153:635–8.
- Irrthum A, Devriendt K, Chitayat D, et al. Mutations in the transcription factor gene SOX18 underlie recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia. *Am J Hum Genet* 2002;72:1470–8.

58. Itin PH, Fistarol SK. Ectodermal dysplasias. *Am J Med Genet* 2004;131C:45–51.
59. Van Steensel MA. Gap junction diseases of the skin. *Am J Med Genet* 2004;131C:12–19.
60. Kelsell D, Dunlop J, Stevens H, et al. Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. *Nature* 1997;387:80–3.
61. Roberts CM, Angus JE, Leach IH, et al. A novel NEMO gene mutation causing osteopetrosis, lymphoedema, hypohidrotic ectodermal dysplasia and immunodeficiency (OL-HED-ID). *Eur J Pediatr* 2010;169(11):1403–7.
62. Clarke A, Phillips DIM, Brown R, et al. Clinical aspects of X-linked hypohidrotic ectodermal dysplasia. *Arch Dis Child* 1987;62:989–96.
63. Rouse C, Siegfried E, Breer W, et al. Hair and sweat glands in families with hypohidrotic ectodermal dysplasia. *Arch Dermatol* 2000;140:850–5.
64. Vanderhooft SL, Stephan MJ, Sybert VP. Severe skin erosions and scalp infections in AEC syndrome. *Pediatr Dermatol* 1993;10:334–40.
65. Cambiaghi S, Tadini G, Barbareschi M, et al. Rapp–Hodgkin syndrome and AEC syndrome: Are they the same entity? *Br J Dermatol* 1994;130:97–101.
66. Vogt BR, Traupe H, Hamm H. Congenital atrichia with nail dystrophy, abnormal facies and retarded psychomotor development in two siblings: A new autosomal recessive syndrome? *Pediatr Dermatol* 1988;5:236–42.
67. Tursen U, Kaya T, Ikizoglu G, et al. Genetic syndrome with ichthyosis: congenital ichthyosis, follicular atrophoderma, hypotrichosis and wooly hair; second report. *Br J Dermatol* 2002;147:604–06.
68. Megarbane H, Zablit C, Waked N, et al. Ichthyosis follicularis, alopecia and photophobia (IFAP) syndrome: report of a new family with additional features and review. *Am J Med Genet* 2004;124A:323–7.
69. Happle R. What is IFAP syndrome? *Am J Med Genet* 2004;124A:328.
70. Oeffner F, Martinez F, Schaffer J, et al. Intronic mutations affecting splicing of MBTPS2 cause ichthyosis follicularis, alopecia and photophobia syndrome. *Exp Dermatol* 2011;20(5):447–9.
71. Boralevi F, Haftek M, Vabres P, et al. Hereditary mucoepithelial dysplasia: clinical ultrastructural and genetic study of eight patients and literature review. *Br J Dermatol* 2005;153:310–18.
72. Korniszewski L, Nowak R, Okniniska-Hoffmann E, et al. Wiedemann–Rautenstrauch (neonatal progeroid) syndrome: New case with normal telomere length in skin fibroblasts. *Am J Med Genet* 2001;103:144–8.
73. Makitie O, Sulisalo T, de la Chapelle A, et al. Cartilage–hair hypoplasia. *J Med Genet* 1995;32:39–43.
74. Pruszkowski A, Bodemer C, Fraïtag S, et al. Neonatal and infantile erythrodermas: a retrospective study of 51 patients. *Arch Dermatol* 2000;136:875–80.
75. Cutrone M, Grimalt R. Transient neonatal hair loss: a common transient neonatal dermatosis. *Eur J Pediatr* 2005;164:630–2.
76. Trakimas C, Sperling LC, Skelton HG, et al. Clinical and histologic findings in temporal triangular alopecia. *J Am Acad Dermatol* 1994;31:205–9.
77. Happle R. Congenital triangular alopecia may be categorized as a paradiagnostic trait. *Eur J Dermatol* 2003;13:346–7.
78. Valari M, Stefanaki C, Karteri G, et al. Tinea capitis due to *Trichophyton rubrum* in a 3-month-old infant. *Mycoses* 2006;49(5):439–40.
79. Rucker Wright D, Gathers R, Kapke A, et al. Hair care practices and their association with scalp and hair disorders in African American girls. *J Am Acad Dermatol* 2011;64(2):253–62.
80. Madsen JT, Bygum A. Trichotillomania in early childhood—a report of two cases with a peculiar habit. *Pediatr Dermatol* 2008;25(5):575–6.
81. Frieden I. Aplasia cutis congenita: a clinical review and proposal for classification. *J Am Acad Dermatol* 1986;14(4):646–60.
82. Schoenfeld RJ, Mehregan AH. Aplastic nevus – the ‘minus nevus’. *Cutis* 1973;12:386–9.
83. Lam J, Dohil MA, Eichenfield LF, et al. SCALP syndrome: sebaceous nevus syndrome, CNS malformations, aplasia cutis congenita, limbal dermoid, and pigmented nevus (giant congenital melanocytic nevus) with neurocutaneous melanosis: a distinct syndromic entity. *J Am Acad Dermatol* 2008;58(5):884–8.
84. Happle R, Horster S. Nevus psiloliparus: report of two nonsyndromic cases. *Eur J Dermatol* 2004;14(5):314–16.
85. Lenane P, Pope E, Krafchik B. Congenital alopecia areata. *J Am Acad Dermatol* 2005;52: S8–11.
86. Xiao FL, Yang S, Liu JB, et al. The epidemiology of childhood alopecia areata in China: a study of 226 patients. *Pediatr Dermatol* 2006;23(1): 13–18.
87. Crowder JA, Frieden IJ, Price VH. Alopecia areata in infants and newborns. *Pediatr Dermatol* 2002;19(2):155–8.
88. Cohen JJ. Hallermann–Streiff syndrome: A review. *Am J Med Genet* 1991;41:488–9.
89. Happle R. Genetic defects involving the hair. In: Orfanos CE, Happle R, editors. *Hair and hair diseases*. Berlin: Springer-Verlag; 1989. p. 345.
90. Baumeister FA, Schwartz HP, Stengel-Rutkowski S. Childhood hypertrichosis: Diagnosis and management. *Arch Dis Child* 1995;72:457–9.
91. Garcia-Cruz D, Figueroa LE, Cantu JM. Inherited hypertrichosis. *Clin Genet* 2002;61: 321–9.
92. Gworys B, Domagala Z. The typology of the human fetal lanugo on the thorax. *Ann Anat* 2003;185:383–6.
93. Felgenhauer WR. Hypertrichosis lanuginosa universalis. *J Genet Hum* 1969;17:1–44.
94. Partridge JW. Congenital hypertrichosis lanuginosa: Neonatal shaving. *Arch Dis Child* 1987;62:623–5.
95. Littler CM. Laser hair removal in a patient with hypertrichosis lanuginosa congenita. *Dermatol Surg* 1997;23:705–7.
96. Salas-Alanis JC, Lopez-Cepeda LD, Elizondo-Rodriguez A, et al. Hypertrichosis lanuginosa congenita treated with diode laser epilation during infancy. *Pediatr Dermatol* 2012; Oct 2, doi: 10.1111/j.1525-4702.2012.01881.x. [Epub ahead of print].
97. Vashi R, Mancini A, Paller A. Primary generalized and localized hypertrichosis in children. *Arch Dermatol* 2001;137:877–84.
98. Barth JH, Wilkinson JD, Dawber RPR. Prepubertal hypertrichosis: Normal or abnormal? *Arch Dis Child* 1988;63:666–8.
99. Gryngarten M, Bedecarrats P, Ayuso S, et al. Clinical assessment and serum hormonal profile in prepubertal hypertrichosis. *Horm Res* 2000;54:20–5.
100. Macias-Flores MA, Garcia-Cruz D, Rivera H, et al. A new form of hypertrichosis inherited as an X-linked dominant trait. *Hum Genet* 1984;66:66–70.
101. Figueroa LE, Pandolfo M, Dunne PW, et al. Mapping of the congenital generalized hypertrichosis locus to chromosome Xq24-q27.1. *Nature Genet* 1995;10:202–7.
102. Baumeister FA, Egger J, Schildhaure MT, et al. Ambras syndrome: Delineation of a unique hypertrichosis universalis congenita and association with a balanced pericentric inversion (8)(p11.2; q22). *Clin Genet* 1993;44:121–8.
103. Tadin-Strapps M, Warburton D, Baumeister FA, et al. Cloning of the breakpoints of a de novo inversion of chromosome 8, inv (8)(p11.2q23.1) in a patient with Ambras syndrome. *Cytogenet Genome Res* 2004;107: 68–76.
104. Sun M, Li N, Dong W, et al. Copy-number mutations on chromosome 17q24.2-q24.3 in congenital generalized hypertrichosis terminalis with or without gingival hyperplasia. *Am J Hum Genet* 2009;84:807–13.
105. Lee IJ, Im SB, Kim DK. Hypertrichosis universalis congenita: A separate entity, or the same disease as gingival fibromatosis? *Pediatr Dermatol* 1993;10:263–6.
106. Kiss P. Gingival fibromatosis, mental retardation, epilepsy and hypertrichosis. *Dev Med Child Neurol* 1990;32:459–60.
107. Lacombe D, Bioulac-Sage P, Sibout M, et al. Congenital marked hypertrichosis and Laband syndrome in a child: Overlap between the gingival fibromatosis-hypertrichosis and Laband syndromes. *Genet Couns* 1994;5:251–6.
108. van Bon B, Gilissen C, Grange D, et al. Cantu syndrome is caused by mutations in ABCC9. *Am J Hum Genet* 2012;90:1094–101.
109. Pivnick EK, Wilroy RS, Martens PR, et al. Hypertrichosis, pigmentary retinopathy and facial anomalies: A new syndrome? *Am J Med Genet* 1996;62:386–90.
110. Jalili IK. Cone-rod congenital amaurosis associated with congenital hypertrichosis: an autosomal recessive condition. *J Med Genet* 1999;26:504–10.
111. Temtamy SA, Sinbawy AH. Cataract, hypertrichosis and mental retardation (CAHMR): a new autosomal recessive syndrome. *Am J Med Genet* 1992;41:432–3.
112. Gleck BJ, Pandya A, Vanner L, et al. Coffin–Siris syndrome: review and presentation of new cases from a questionnaire study. *Am J Med Genet* 2001;99:1–7.
113. McGhee EM, Klump CJ, Bitts SM, et al. Candidate region for Coffin–Siris syndrome at 7q32–34. *Am J Med Genet* 2000;93:241–3.
114. Roth SI, Schedewie HK, Herzberg VK, et al. Cutaneous manifestations of leprechaunism. *Arch Dermatol* 1981;117:531–5.
115. Hsiung SH. Rubinstein–Taybi syndrome (broad thumb–hallux syndrome). *Dermatol Online J* 2004;10:2.
116. Roelfsema J, White J, Ariyurek Y, et al. Genetic heterogeneity in Rubinstein–Taybi syndrome: mutations in both the CBP and EP300 genes cause disease. *Am J Hum Genet* 2005;76: 572–80.
117. Santana SM, Alvarez FP, Frias JL, et al. Hypertrichosis, atrophic skin, ectropion and macrostomia (Barber–Say) syndrome: Report of a new case. *Am J Med Genet* 1993;47:20–3.
118. Kvigne VL, Leonardson GR, Neff-Smith M, et al. Characteristics of children who have full

- or incomplete fetal alcohol syndrome. *J Pediatr* 2004;145:635–40.
119. Kaler SG, Patrinos ME, Lambert GH, et al. Hypertrichosis and congenital anomalies associated with maternal use of minoxidil. *Pediatrics* 1987;79:434–6.
120. Vergani R, Betti R, Martino P, et al. Giant nevoid hypertrichosis in an Iranian girl. *Pediatr Dermatol* 2002;19:64–6.
121. Knable A, Treadwell P. Pigmented plaque with hypertrichosis on the scalp of an infant. *Pediatr Dermatol* 1996;13:431–3.
122. Glover MT, Malone M, Atherton DJ. Michelin-tire baby syndrome resulting from diffuse smooth muscle hamartoma. *Pediatr Dermatol* 1989;6:329–31.
123. Danarti R, Konig A, Salhi A, et al. Becker's nevus syndrome revisited. *J Am Acad Dermatol* 2004;51:965–9.
124. Ferreira MJ, Bajanca R, Fiadeiro T. Congenital melanosis and hypertrichosis in a bilateral distribution. *Pediatr Dermatol* 1998;15:290–2.
125. Johnson MD, Jacobs AJ. Congenital smooth muscle hamartoma. *Arch Dermatol* 1989;125:820–2.
126. Gagne EJ, Su WP. Congenital smooth muscle hamartoma of the skin. *Pediatr Dermatol* 1993;10:142–5.
127. Ettl A, Marinkovic M, Koornneef L. Localized hypertrichosis associated with periorbital neurofibroma; clinical findings and differential diagnosis. *Ophthalmology* 1996;103:942–8.
128. Pivnik EK, Lobe TE, Fitch SJ, et al. Hair whorl as an indicator of a mediastinal plexiform neurofibroma. *Pediatr Dermatol* 1997;14:196–8.
129. Flannery DB, Howell CG. Confirmation of the Riccardi sign. *Proc Greenwood Genet Centre* 1986;6:161.
130. Wong SN, Tay YK. Tufted angioma: a report of five cases. *Pediatr Dermatol* 2002;19:388–93.
131. Herron M, Coffin CM, Vanderhooft SL. Tufted angiomas: variability of the clinical morphology. *Pediatr Dermatol* 2002;19:394–401.
132. Guggisberg D, Hadj-Rabia S, Viney C, et al. Skin markers of occult spinal dysraphism in children. *Arch Dermatol* 2004;140:1109–15.
133. Drolet B. Cutaneous signs of neural tube malformations. *Semin Cutan Med Surg* 2004;23:125–37.
134. Schropp C, Sorensen N, Collmann H, Krauss J. Cutaneous lesions in occult spinal dysraphism – correlation with intraspinal findings. *Childs Nerv Syst* 2006;22(2):125–31.
135. Reed OM, Mellette JR, Fitzpatrick JE. Familial cervical hypertrichosis with underlying kyphoscoliosis. *J Am Acad Dermatol* 1989;20:1069–72.
136. Herron M, Coffin CM, Vanderhooft SL. Vascular stains and hair collar sign associated with congenital anomalies of the scalp. *Pediatr Dermatol* 2005;22:200–5.
137. Stone N, Burge S. Focal facial dermal dysplasia with a hair collar. *Br J Dermatol* 1998;139:1136–7.
138. Wells JM, Weedon D. Focal facial dermal dysplasia or aplasia cutis congenita: a case with a hair collar. *Australas J Dermatol* 2001;42:129–31.
139. Penas PF, Jones-Caballero M, Garcia-Diez A. Cutaneous heterotopic meningeal nodules. *Arch Dermatol* 1995;131:731.
140. Cox NH, McClure JP, Hardie RA. Naevoid hypertrichosis – report of a patient with multiple lesions. *Clin Exp Dermatol* 1989;14:62–4.
141. Rogers M. Naevoid hypertrichosis. *Clin Exp Dermatol* 1981;16:74.
142. Cheung ST, Lanigan SW. Naevoid hypertrichosis treated with alexandrite laser. *Clin Exp Dermatol* 2004;29:435–6.
143. Akarsu S, Coskun BK, Aydin AM, et al. Congenital hemihypertrophy with hemihypertrichosis. *J Dermatol* 2005;32:478–81.
144. Bragonier R, Karabouta Z, Crowne L. Transient scrotal hair growth in infancy. *Postgrad Med J* 2005;81:412.
145. Braddock SR, Jones KL, Bird LM, et al. Anterior cervical hypertrichosis: A dominantly inherited isolated defect. *Am J Med Genet* 1995;55:498–9.
146. Trattner A, Hodak E, Sagie-Lerman T, et al. Familial congenital anterior cervical hypertrichosis associated with peripheral sensory and motor neuropathy associated with anterior cervical hypertrichosis. *J Pediatr Ophthalmol Strabismus* 1997;34:309–12.
147. Garty BZ, Snir M, Kremer I, et al. Retinal changes in familial peripheral sensory and motor neuropathy associated with anterior cervical hypertrichosis. *J Pediatr Ophthalmol Strabismus* 1997;34:309–12.
148. Jackson CE, Callies QC, Krull EA, et al. Hairy cutaneous malformations of the palms and soles. *Arch Dermatol* 1975;111:1146–9.
149. Visser R, Beemer FA, Veenhoven RH, et al. Hypertrichosis cubiti: Two new cases and a review of the literature. *Genet Couns* 2002;13:397–403.
150. MacQuillan A, Hamilton S, Grobbelaar, A. Angiosomes, clefts, and eyelashes. *Plast Reconstr Surg* 2004;113:1400–3.
151. Brooks BP, Dagenais SL, Nelson CC, et al. Mutation of the FOXC2 gene in familial distichiasis. *J Am Assoc Pediatr Ophthalmol Strabismus* 2003;7:354–7.
152. Lee AC, Kamalam A, Adams SM, et al. Molecular evidence for absence of Y-linkage of the Hairy Ears trait. *Eur J Hum Genet* 2004;12:1077–9.

Nail Disorders

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Introduction

Nails are specialized cutaneous appendages composed of hard keratins similar to those found in hair, and are unique to primates. In humans, nails function as a stabilizing unit to aid in tactile sensation, grasping, and scratching. Well-manicured or adorned nails in adolescents and adults may be perceived as an attribute of social acceptability and serve as a source of personal satisfaction. Although abnormalities of the nails are rare, they may affect an individual's self-esteem and their relationships with others. Abnormal nails in a neonate or infant may be indicative of a more widespread inherited or sporadic syndrome, or they may be a localized congenital malformation. In either case, parents may be concerned about their child's nails, sometimes out of proportion to the magnitude of any other problems that may be present. Investigation and consultations to uncover any associated illness and to allay any untoward parental anxiety are warranted.

The nail unit is composed of a rectangular nail plate bordered by proximal and lateral nail folds (Fig. 32.1).¹ The cuticle attaches the proximal nail fold to the nail plate. This acellular membrane is tightly adherent and prevents invasive microorganisms reaching the underlying matrix. The lunula (half moon) represents the distal portion of the nail's proliferative matrix. The ventral side of the nail plate has longitudinal ridges that orient the direction of growth from the root over a complementary grooved nail bed. At birth, the dorsal surface of the nail displays unique, somewhat oblique ridges as well. These ridges become parallel and disappear slowly, and over time, the surface becomes smooth. The distal free edge of the plate separates from the bed at the hyponychium. The shape of the nail plate is convex. It is normally thickest at its proximal portion and thins distally. The size of the nail plate is determined by the size and growth of the underlying distal phalanx. Because embryologic development occurs in a cephalocaudal direction, it is not surprising that at birth, especially in premature infants, toenails may be smaller than fingernails. In premature infants, less than 32 weeks' gestation, nail plates may not extend beyond the distal groove of the hyponychium. In postmature infants, such as macrosomic infants or infants of diabetic mothers, the nail plate may extend well beyond the hyponychium. In adults, it is estimated that fingernails grow 0.1 mm/day and toenails grow 1 mm/month. Similar data in newborns and infants are not available. Box 32.1 lists pathologic factors that affect nail growth.

The anatomic structure of the nail unit is affected by many disease states.¹ Conditions may be primary or secondary, localized or generalized, congenital or acquired. They can be associated with genetic syndromes, or drug exposures, or with infectious or systemic disease. Nail morphogenesis begins during the 9th week of gestation and is completed by the end of the second trimester (see Chapter 1).

Beau's lines

Beau's lines are transverse grooves or moat-like depressions that extend across the nail plate from one lateral nail fold to the other.^{2,3} This deformity is a manifestation of nail matrix arrest and is first observed adjacent to the proximal nail fold. Beau's lines slowly move toward the distal free edge of the nail plate as nail growth resumes. If the rate of nail growth is known, one can estimate the date of nail matrix arrest by measuring the distance between the proximal nail fold and the Beau's line. Causes of Beau's lines include high fevers caused by infection, severe cutaneous inflammatory diseases such as Stevens-Johnson syndrome or Kawasaki disease, a reaction to medications, and acrodermatitis enteropathica. Beau's lines may occur in infants, 4–10 weeks of age, as a result of the stress of delivery. They have also been reported at birth as a result of intrauterine stress in a premature infant (Fig. 32.2).⁴ Although Beau's lines should develop on all fingernails and toenails, they are usually most prominent on the thumb and great toe nails because of their slower rate of growth.

Onychomadesis refers to proximal separation of the nail plate from the nail bed. Latent onychomadesis occurs when the nail separates some time after a profound interruption in nail growth. Causes are similar to those that produce Beau's lines and may occur during the neonatal period as well.

Alterations in nail shape

There is a close interaction between the formation of epidermal appendages and mesoderm during embryologic development. Therefore, it is not surprising that there are many alterations of nail shape that are linked with distant or underlying malformations of bone. It is not uncommon for newborns to have variations of the normal convex curvature of the nail. Koilonychia refers to nails that exhibit a concave or spoon shape.⁵ This may be a normal variant in newborns, especially when it involves the great toe nails. As the child grows and the distal phalanges lengthen, koilonychia gradually improves. Recently, a case of koilonychia, dome-shaped femoral epiphyses, and platyspondylia has been described.⁶ It is widely accepted that koilonychia in infants and toddlers may be indicative of iron deficiency.⁷ However, no well-controlled studies of iron deficiency in large numbers of infants with and without koilonychia have been reported, and improvement of nail shape with the administration of iron has not been documented. Familial koilonychia has also been reported.⁸ It has been described with other ectodermal defects such as monilethrix, palmoplantar keratoderma, and steatocystoma multiplex, as well as Turner syndrome.⁹

Other deformities in nail shape include pincer nails, claw nails, and racquet nails. Pincer nails are characterized by a transverse overcurvature of the nail plates.¹⁰ The condition is

usually acquired, but some cases may result from an inherited developmental anomaly. If the convex transverse overcurvature is prominent, nails may appear similar to those in patients with pachyonychia congenita and occasionally may be quite painful. Congenital claw-like nails have also been reported.¹¹ The nail

BOX 32.1 PATHOLOGIC FACTORS THAT ALTER NAIL GROWTH

SLOWER

- Severe infections
- Prolonged illness
- Hypothyroidism
- Malnutrition
- Congestive heart failure
- Ischemia
- Nerve injury

FASTER

- Arteriovenous shunts
- Erythroderma
- Hyperthyroidism

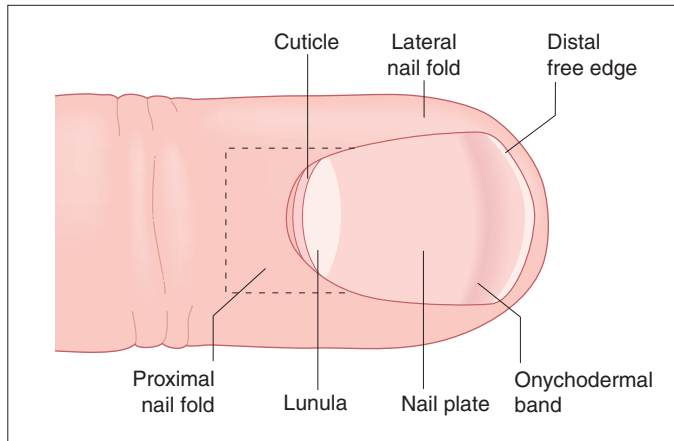


Figure 32.1 Dorsal view of the nail unit. (Reproduced with permission from Gonzales-Servas A. Scher & Daniel: *Nails: therapy, diagnosis, surgery*. 2nd ed. New York: WB Saunders; 1997.)



Figure 32.2 Beau's lines are transverse grooves of the nail plate that represent a brief reduction of growth from the nail matrix.

plates have a dorsal convexity and then curve downward to resemble onychogryphosis. This is usually noted on the second to fourth toes and may be associated with a cleft hand. Hypoplasia of the distal phalanx with absence of the ossification center is observed on radiographs of the affected digits.¹² Correction of the deformity is desirable because of the tendency toward recurrent bleeding and ulceration of the tip of the toe. Some authors distinguish claw nails from another isolated ungual anomaly, congenital curved nail of the fourth toe.¹³ Nails in these cases are normal thickness and have a longitudinal overcurvature. This trait may be sporadic or inherited, and is also associated with underlying distal phalangeal deformities.¹⁴ It may not come to medical attention until traumatic dystrophy occurs later in childhood. Racquet nails occur when the width of the nail plate exceeds its length, also referred to as brachyonychia. It may be a sign of foreshortening of the terminal phalanx and may be associated with other congenital anomalies.¹⁵

Clubbing is a curved or beak-like deformity of the nail unit that accompanies hypertrophy and hyperplasia of the fibrovascular support stroma of the distal phalanx. It is an acquired sign of both systemic and hereditary diseases.¹ In neonates or infants, clubbing may be an early manifestation of cyanotic congenital heart disease, bronchopulmonary diseases, or HIV disease.^{16,17}

Alterations in nail size

Anonychia refers to the absence of nails. The most widely known association is with nail–patella syndrome (see below). Isolated congenital anonychia has been reported in families with both autosomal recessive^{18,19} and autosomal dominant inheritance. Rudimentary nail units may be evident, but the underlying phalangeal structure is normal. Anonychia and hypoplasia of the nails may be observed with absence of the distal phalanges and foreshortening of the affected digits (Fig. 32.3). Anonychia has been reported with limb defects,²⁰ ectrodactyly,²¹ flexural pigmentation,²² isolated to the thumbnails,²³ and with sensorineural hearing loss.²⁴ These latter cases have been termed DOOR syndrome (deafness, onychosteodystrophy, and retardation). Elevated urinary amino acids

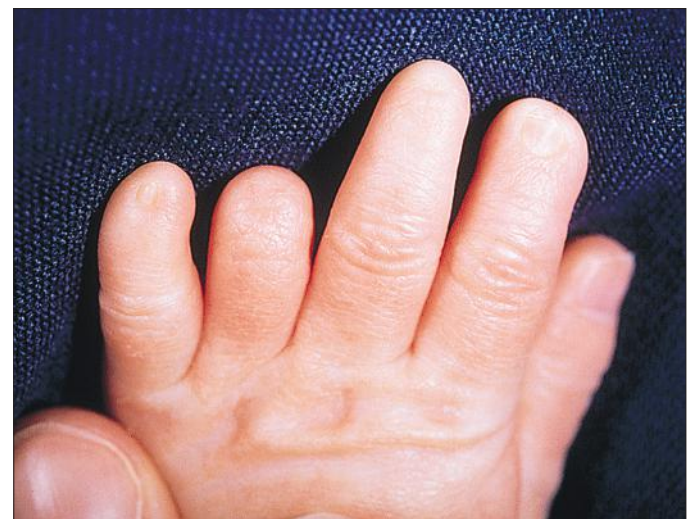


Figure 32.3 Anonychia with absence of the distal phalanx and foreshortening of the digit.

have been detected in some patients with DOOR syndrome.²² Anonychia of the fifth fingers and toenails is characteristic of Coffin–Siris syndrome.²⁵ Other features include growth and mental retardation, generalized hypertrichosis and scalp hypotrichosis, lax joints, and abnormal facies. Anonychia, nail hypoplasia, and other nail anomalies, such as double nails (Fig. 32.4), may occur as isolated findings.²⁶

Infants with junctional and dystrophic forms of epidermolysis bullosa (EB) frequently have anonychia at birth (Fig. 32.5).²⁷ Subungual hemorrhages, onycholysis (separation of the nail plate from the nail bed) and onychomadesis precede nail loss. One or more fingernails are usually affected. The periungual tissues and nail beds are frequently swollen and inflamed. Granulation tissue develops quickly. Meticulous hygiene, application of topical antibiotics, and wound care with synthetic dressings may optimize regrowth if possible. It is the authors' opinion that in utero sucking of the fingers results in most of the nail disease that is present at birth in EB.



Figure 32.4 Double nail anomaly.



Figure 32.5 Anonychia of the index finger in a case of junctional epidermolysis bullosa.

Micronychia

Small nails may be localized to one or a few digits or involve all of the nail fields (Fig. 32.6). Conditions associated with micronychia are listed in Table 32.1.^{28–32} Current theory suggests that at least some forms of micronychia, such as in fetal alcohol syndrome and exposure to anticonvulsants, are due to inhibition of retinoic acid synthesis during early embryologic development.^{33,34} Selected specific causes of micronychia are discussed in subsequent sections.

Nail–patella syndrome

Nail–patella syndrome, also known as hereditary osteo-onychodysplasia (HOOD), is an autosomal dominant genodermatosis characterized by nail hypoplasia present at birth, chronic progressive nephropathy, and hypoplastic patellae that may result in debilitating osteoarthritis. This disorder has a high degree of penetrance and widely variable expressivity.³⁵ Nail disease is usually the only manifestation in neonates. However, there are rare reports of infants with proteinuria, signifying the early onset of renal pathology.³⁶

Ungual manifestations are most prominent on the ulnar sides of the thumbs and index fingers, and to a lesser degree on other digits. They include micronychia, hemionychia, and occasionally anonychia. If present, a triangularly shaped lunula with a distal apex is nearly pathognomonic for the condition.³⁷ Nail plates may be thin and display koilonychia, which can lead to frequent chipping and splitting later in childhood.

Skeletal deformities are not visible until ossification centers develop. Parents may be screened for small, easily subluxed patellae, characteristic posterior iliac horns, hypoplasia of the proximal radius and ulna, scoliosis, and thickened scapulae. Generally, patients with nail–patella syndrome are not identified until early adulthood, when knee dislocation, pain, and gait disturbances bring them to medical attention.³⁸

Renal disease that presents as asymptomatic proteinuria is the most serious manifestation of nail–patella syndrome. It is usually not apparent until adulthood, but a newborn and a 2-year-old child with nephrosis have been reported.³⁹ Renal biopsies have uncovered glomerulonephritis secondary to



Figure 32.6 Micronychia in an otherwise well child.

TABLE
32.1

Causes of micronychia

Disorder	Clinical manifestations
Nail-patella syndrome	Small or absent patellas, iliac horns, triangular lunulae
Congenital onychodysplasia	
Ectodermal dysplasias	Variable sweating, hair and tooth abnormalities
Congenital malalignment of index fingers	None, except underlying phalangeal malformation
Fetal teratogens	
Alcohol	Microcephaly, short palpebral fissures, maxillary hypoplasia
Hydantoins (and other anticonvulsants)	Short stature, retardation, hypertelorism, depressed nasal bridge, cardiac anomalies, mucosal changes
Polychlorinated biphenyls	Natal teeth, pigment anomalies, mucosal changes
Warfarin	Nasal hypoplasia, stippled epiphyses
Chromosome and genetic abnormalities	
Coffin–Siris syndrome	Hypoplasia of the fifth digit, lax joints, blepharoptosis, and multiple genetic mutations
Dyskeratosis congenita	Hyperpigmentation and hypopigmentation, Fanconi-like anemia, blepharitis, leukoplakia, XLR ^a and <i>DKC1</i> mutation
Adams–Oliver syndrome	Large defects of aplasia cutis of the scalp with cutis marmorata, congenital heart malformations and transverse limb reduction defects, <i>DOCK6</i> and <i>RBPJ</i> mutations
Simpson–Golabi–Behmel syndrome	Macrosomia, abnormal facies, supernumerary nipples, polydactyly, heart defects, X-linked <i>GPC3</i> mutation
Trisomies	3q, 8, 13, 18
Turner syndrome	XO, webbed neck, nevi, lymphedema, coarctation of the aorta
Noonan syndrome	XY male with a Turner phenotype and pulmonic stenosis
Amniotic bands	Hypoplasia of the distal phalanx associated with aplasia cutis

^aX-linked recessive inheritance.

glomerular basement membrane zone thickening from collagen fibril deposition. These findings have even been noted in a spontaneously aborted 18-week-old fetus.⁴⁰

Other manifestations include heterochromic irides, colobomas, microcorneas, glaucoma,⁴¹ popliteal pterygia, and mild mental deficiency. It has been suggested that these, as well as other findings such as colon cancer, in specific kindreds may be a result of contiguous gene defects, translocations, or other genetic aberrations.⁴² Complications from cerebral and large vessel dilation have also been reported, and are also caused by collagenous basal lamina reduplication.⁴³

Mutations in the LIM homeodomain protein gene *LMX1b* have been demonstrated in the region of 9q34 and result in the nail–patella syndrome.⁴⁴ This gene is responsible for dorsoventral body pattern formation during fetal development. It is linked to the ABO blood group and had been believed to be an abnormality in *COL5A1*, which is necessary for the production of collagen type V, an important component in the glomerular and other basement membrane zones.⁴⁵

Congenital onychodysplasia of the index fingers

Congenital onychodysplasia of the index fingers (COIF), also now known as Iso–Kikuchi syndrome, was first described in 1969.^{46,47} Original cases were congenital, limited mainly to the index fingers, and characterized by anonychia, micronychia, and/or polyonychia (Fig. 32.7). They were nonfamilial and nonhereditary, and without underlying bone or joint abnormalities. Since that time, the clinical criteria have been changed or expanded to encompass a number of additional observations.⁴⁸

Although the index fingers are most commonly affected, onychodystrophy has been reported on other fingers and toes.^{49,50} Malalignment, ‘rolled micronychia,’ hemionychogryphosis, onychoheterotopia, and polyonychia with syndactyly have also been detailed. Unlike nail–patella syndrome,



Figure 32.7 Absence or hypoplasia of the nail unit of the index fingers is characteristic of congenital onychodysplasia of the index fingers.

abnormalities in the nail unit are more prominent on the radial aspects of the digits. A Y-shaped bifurcation of the distal phalanx on lateral radiographs is frequent and is characteristic of the condition.⁵¹ Familial cases have also been documented.⁵²

The pathogenesis of congenital onychodysplasia is poorly understood. An abnormal vascular supply, anomalies from an abnormal grip, external deformation from pressure against the cranium, exposure to teratogens, and genetic influences have been implicated by a number of authors.⁵⁰ It is quite possible that the clinical findings may be explained by any of these theories if the inciting event occurs at a specific time during the embryologic development of the nail unit.

Onychoatrophy

Onychoatrophy refers to a progressive reduction in size and thickness of the nail unit. The term is usually used to describe acquired dissolution of ungual structures and should not be used synonymously with micronychia, although some authors do so. Inflammatory disorders, which are observed in older children and adults, but rarely documented in newborns and infants, such as Stevens–Johnson syndrome or graft-versus-host disease, may result in onychoatrophy. Infants with congenital disorders that have a progressive phenotype, such as acrogeria or dyskeratosis congenita, can have onychoatrophy as well. Occlusion of the digital artery by emboli may result in phalangeal necrosis and destruction of nail structures. Other postnatal vascular insults, such as extensive aplasia cutis congenita or disseminated intravascular coagulation from homozygous protein C deficiency, could potentially have similar effects.

Ectopic nails

Onychoheterotopia, or ectopic nails, occurs when ungual tissue develops on areas other than the dorsal aspect of the distal phalanx.⁵⁰ Cases that have been reported tend to involve the palmar surface of the fifth fingers.^{53–56} They have been both sporadic and reported in siblings, suggesting possible autosomal recessive inheritance. Other abnormalities of the hand may also be present, including underlying osseous malformations. A circumferential nail of the fifth finger has been documented in association with a deletion in the long arm of chromosome 6.⁵⁷ This tubular defect may occur on other digits as well.⁵⁸ The presence of a circumferential nail is frequently observed at the tip of the fused digits of the hand in acrocephalosyndactyly or Apert syndrome.⁵⁹ Synonychia and fusion of all of the toes are also observed in this sporadic condition, which is caused by mutations in the gene encoding fibroblast growth factor receptor-2 (*FGFR-2*) found on the chromosomal locus 10q26 (Fig. 32.8).⁶⁰

Hypertrophy of the nail

Large nails with anatomically normal nail units may be observed in newborns with macrodactyly. Conditions that display macronychia include epidermal nevus syndrome, Proteus syndrome, Maffucci syndrome, Klippel–Trenaunay–Weber syndrome, and gigantism. Patients with the ectrodactyly–ectodermal dysplasia–cleft lip/palate (EEC) syndrome also may have a large nail on the fused digits. Several terms are used to describe different types of enlarged nails. Onychauxis refers to nails that exhibit thick nail plates but retain a normal overall size and shape. Onychogryphosis is present when the nail plate thickens and develops an inferior overcurvature. If nail growth is uneven, the plate deviates obliquely and takes on the appearance of a ram's horn. The nail plates are usually discolored and display oyster-like striations across the surface. Although onychogryphosis is usually observed on toenails in the elderly or on digits that have been permanently injured, hereditary autosomal dominant and congenital forms involving both the fingernails and toenails have been reported.^{53,54} Hemionychogryphosis has been seen in cases of congenital malalignment of the great toe nails and COIF. Pachyonychia refers to thickening and superior deviation of the nail plate owing to the accumulation of subungual hyperkeratosis. This may be observed in older patients with psoriasis

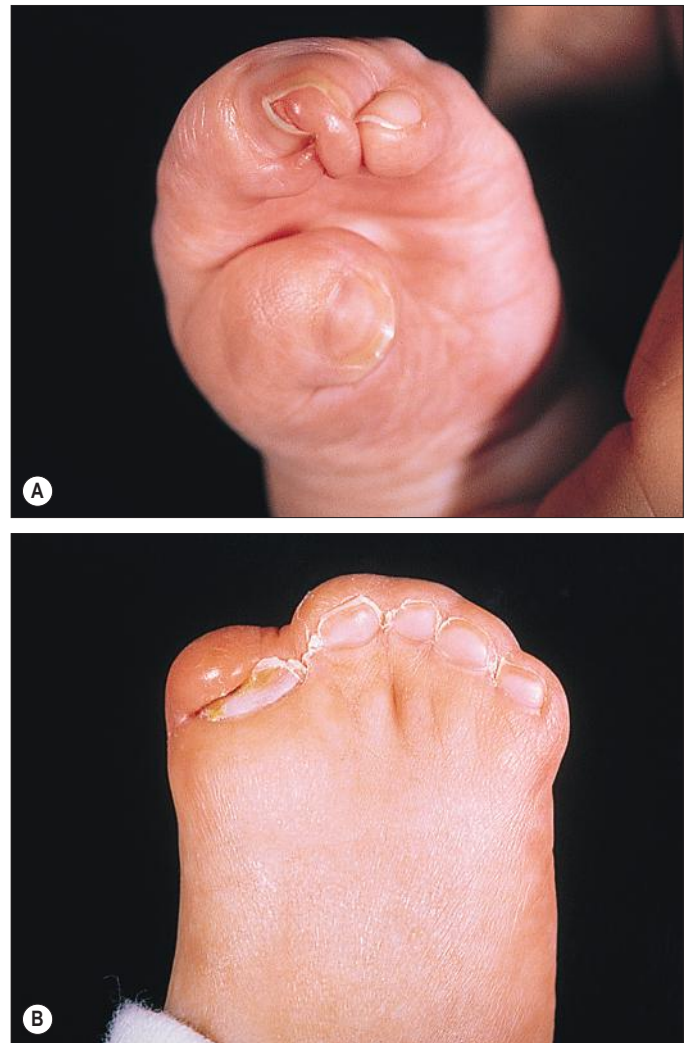


Figure 32.8 (A) Fused second to fourth digits of the hand of a patient with Apert syndrome who had a single circumferential nail. (B) Synonychia and syndactyly of the toes in a patient with Apert syndrome.

or onychomycosis, but the term is classically used to describe the inherited condition pachyonychia congenita.

Pachyonychia congenita

Pachyonychia congenita⁶¹ is characterized by hard, thick nails that angle upwards at their distal free edge because of accumulation of keratin in the ventral nail plate. The lateral borders curve under and give the plates a pincer-like appearance (Fig. 32.9). Unlike onychogryphosis, the nails of pachyonychia congenita have a smooth surface. Although pachyonychia congenita syndrome is transmitted as an autosomal dominant trait with a high degree of penetrance, full expressivity may not become evident until later childhood or adulthood. Infants with pachyonychia congenita initially display a yellowish-brown discoloration of the nails. Thickening from subungual hyperkeratosis occurs gradually over months to years.

Until recently, patients with pachyonychia congenita were classified into one of two syndromes that had one of several genetic defects in hard keratin.⁵⁵ Mutations in keratin 16 (located on chromosome 17) or in keratin 6A (located on



Figure 32.9 Pachyonychia congenita. Pincer appearance of nails.



Figure 32.10 Pachyonychia congenita. White oral mucosal leukokeratotic plaques.

chromosome 12) have been found in type I, the Jadassohn–Lewandowski variant. As newborns, these patients may have foamy white mucosal plaques of oral leukokeratosis (Fig. 32.10). During childhood, debilitating palmoplantar keratoderma, hyperhidrosis, and secondary bullae develop. Clusters of rough, dry, spiny papules become evident over the body, particularly on the elbows and knees, similar to psoriasis. Later, there may be eruption of epidermoid cysts. Type II patients with the Jackson–Lawler form of the disease have abnormalities in the keratin 17 gene (found on chromosome 17) or keratin 6B (found on chromosome 12). Natal teeth with milia, minimal oral leukokeratosis, cylindromas, steatocystomas, and milder keratoderma are present in these cases. However, considerable overlap may exist with some signs.

A recent publication from the International Pachyonychia Congenita Consortium (IPCC) recommends the elimination of the terms ‘PC-1’ and ‘PC-2’ and proposed their replacement with notation of the specific keratin defect. In this classification scheme a diagnosis of PC-6a, PC-6b, PC-16, and PC-17 would correspond to mutations in the *KRT6A*, *KRT6B*, *KRT16*, and *KRT17* genes, respectively. A designation of PC-U (unknown) may be applied when the classic clinical findings of PC are



Figure 32.11 Ingrown nails characterized by erythema and swelling of the medial nail folds in a case of congenital malalignment of the great toe nails.

found in the absence of a known PC keratin gene mutation. This new classification recognizes the overlap in signs and symptoms of the different genotypes of PC and will aid in future gene therapy for these patients.⁶¹ A registry and support group for patients and their families with pachyonychia congenita is now available (www.pachyonychia.org).

Ingrown toenails

There are three types of ingrown toenail in neonates. Congenital malalignment of the great toe presents with a trapezoid-shaped nail plate that deviates laterally with respect to the longitudinal axis of the distal phalanx (Fig. 32.11).⁵⁶ Cases may be unilateral, bilateral, sporadic, or inherited as an autosomal dominant trait.⁵⁷ While classically affecting the great toes, malalignment of the fourth toenail and index fingers has also been reported.^{62,63} Recurrent damage to the nail matrix occurs when the child is old enough to crawl and walk. This damage is manifested by multiple transverse ridges, discoloration caused by infection and hemorrhage, paronychia, onycholysis, and nail loss.⁵⁸ Mild degrees of malalignment may improve over time.⁵⁹ However, when marked deviation of the nail plate results in the distal free edge embedding into the soft tissues of the hyponychium, surgical rotation of the misdirected matrix may be necessary to prevent chronic long-term disability.⁶⁰

Congenital hypertrophy of the lateral nail folds of the hallux may present at birth or in the first month of life as red, firm, enlarged masses of tissue that may cover significant amounts of the nail plate.⁶⁴ If the induration persists, it may become painful or infected when the infant begins to crawl or walk. The condition usually remits spontaneously. A 2-week trial of a potent topical steroid solution (e.g., fluocinonide 0.05% twice daily) would not be unreasonable if surgical reduction of the excess tissue is contemplated.

Embedding of the distal free margin of the nail plate into the soft tissue of the hyponychium is not uncommon. A prominent ridge of tissue may form a wall that results in embedding or superior deflection of the nail plate. Most neonates outgrow these findings by 6 months of age.⁶⁵ Some authors believe that factors such as sleeping prone, especially when the child begins to kick actively, and tight-fitting sleepsuits may predispose the older infant to paronychia.⁶⁶

Paronychia and infectious nail dystrophy

Infections of the nail unit in neonates are extremely important to identify and treat promptly because of the possibility of irreversible damage to the nail matrix. Once the protective cuticle or hyponychium are compromised, then the matrix, an area of relative immune privilege, can be easily invaded.⁶⁷ Acute paronychia presents with red, swollen, tender nail folds. Purulent material accumulates in the periungual groove and can extend under the nail plate. Chronic paronychia manifests with painless swelling of the nail fold, loss of the cuticle, and the development of granulation tissue. Organisms responsible for paronychia include *Candida* spp.,⁶⁸ *Staphylococcus*, *Streptococcus*, *Veillonella* (in neonates),⁶⁹ anaerobes, saprophytes, and herpes simplex. Paronychia is most common on the fingers as a result of developmentally appropriate sucking or mouthing of the digits. Systemic diseases associated with paronychia include mucocutaneous candidiasis, DiGeorge syndrome, acrodermatitis enteropathica, Langerhans' cell histiocytosis,⁷⁰ and HIV infections.⁷¹ Once diagnostic tests have been completed (e.g., cultures, Gram stain, potassium hydroxide preparation, and Tzanck preparation), treatment can be started. Burow's solution soaks aid in gentle debridement of infected tissues. In mild cases, twice-daily use of topical solutions such as clindamycin or clotrimazole is indicated. Several days of concomitant applications of a topical steroid solution may reduce any pain and swelling. In more severe cases, purulent material may have to be surgically drained and granulation tissue may need to be cauterized.

Onychomycosis

Onychomycosis is rare in neonates and infants yet the literature documents many case reports of dermatophyte infection occurring in the first few months of life.^{2-4,72} Tinea unguium may be less prevalent in this age group because of faster linear nail growth and subsequent elimination of fungi, a smaller contact surface, a lower incidence of tinea pedis, and less frequent exposure to fungi in public areas.⁷³⁻⁷⁵ A series of 16 patients under 2 years of age included seven cases of Down syndrome, two cases associated with preterm birth, and two others with perinatal hypoxia.⁷⁶ There was a strong association of concomitant fungal infection in the families, with 14/16 fathers and 7/16 mothers having tinea pedis or onychomycosis. Toenails were more affected than fingernails. However, fingernail involvement is more common in young children than in adults.⁷⁷

It is not surprising that *Candida* can affect neonates, as *Candida* species are known to be abundant in their environment, mostly affecting the skin and mucosa, and not the nails.⁷⁸ In the neonatal and infant population, candidal onychomycosis has been documented to be caused by *Candida albicans*,⁷⁹ *Candida parapsilosis*,⁸⁰ and *Candida tropicalis*.⁷⁸ Congenital candidiasis localized to the nails has been reported in premature and term newborns (Fig. 32.12).^{79,81} A potential source of infection is maternal vulvovaginitis, which may be asymptomatic, or associated with vaginal discharge that has resolved by the time nail changes are noted. Therefore, it is prudent to inquire about potential symptoms. In neonates, nail candidiasis has been associated with congenital cutaneous candidiasis.^{68,81,82} A series of six cases of isolated congenital nail candidiasis without other associated skin findings has been reported.⁸³ In three cases,



Figure 32.12 Onychomycosis due to congenital candidiasis is characterized by punctate leukonychia, pits, brittleness, and chipping of the surface of the nail plate. (Courtesy Dr Lloyd Krammer, INOVA Fairfax Hospital for Children.)

Candida vaginitis was diagnosed during the third trimester of pregnancy. Nail changes were noted at birth in two cases, and shortly afterwards (3 weeks to 1.5 months of life) in the remaining cases. All six had involvement of multiple fingernails, and in two cases, several toenails were affected as well. None were immunosuppressed or had chronic mucocutaneous disease.

Clinical features of onychomycosis in the neonate and infant are identical to those seen in older patients. Dystrophy includes thickening, a yellow discoloration, and subungual debris. White superficial onychomycosis has also been reported.⁸⁴ Latent onychomadesis secondary to candidiasis has also been observed.⁸⁵

A definitive diagnosis should be made before any treatment of neonatal onychomycosis. Either clippings sent for histology, fungal cultures, or potassium hydroxide preparations obtained by gentle curettage with a serrated curette can establish a diagnosis. Documentation of infection is important, especially when multiple nails are involved, since psoriasis, lichen planus, trachyonychia, yellow nail syndrome, and pachyonychia congenita are in the clinical differential diagnosis.

Topical therapy should be considered initially because of the lack of potential systemic side effects. It may work well in young children because of their relatively thin nail plates as well as presumed faster nail growth. There are neither published guidelines nor FDA approved medications for the treatment of onychomycosis in this age group. Topical antifungal agents including ciclopirox and amorolfine lacquers as well as bifonazole-urea ointment under occlusion can be successful^{76,86} over 6–12 weeks.⁸⁷ Congenital candidal nail infection also responds to topical therapy. Agents reported to be successful include ciclopirox olamine 8% nail lacquer,⁷⁹ clotrimazole 1% cream, ciclopirox olamine 1% cream, or combinations of the products. It should also be noted that at least one case of candida onychomycosis resolved spontaneously, after several months without any treatment.⁷⁸

If oral medication with itraconazole, fluconazole or terbinafine is considered for refractory cases, monthly laboratory monitoring should be considered. An 8-week-old infant with *Trichophyton rubrum* affecting 18 nails responded to a combination of 8% ciclopirox nail lacquer and oral terbinafine at a dose of 25 mg/day; the infant weighed 6 kg.⁸⁸ A premature

BOX 32.2 CAUSES OF ONYCHOLYSIS**SYSTEMIC**

- Thyroid disease
- Iron deficiency
- Erythropoietic protoporphyria

CONGENITAL/HEREDITARY

- Partial hereditary onycholysis
- Ectodermal dysplasias
- Periodic shedding of the nails
- Leprechaunism

PRIMARY SKIN DISEASES

- Epidermolysis bullosa
- Psoriasis

MEDICATIONS^a

- Indomethacin
- Retinoids
- Antibiotics
- Chemotherapy

LOCAL CAUSES

- Thermal injury (pulse oximeters)
- Trauma

INFECTIONS

- *Candida*

^aDirectly or in combination with ultraviolet light (photo-onycholysis).

Modified from Baran R, Dawber RPR. *Diseases of the nails and their management*. 2nd ed. Oxford: Blackwell Scientific Publications; 1994:59.

infant that developed onychomycosis caused by *Candida parapsilosis* that affected multiple fingernails and toenails was treated successfully with systemic fluconazole 5 mg/kg per day for 30 days and topical ketoconazole once per day for 6 months,⁸⁰ with a clinical response within 7 weeks.

Choice of potential therapies for onychomycosis in the neonatal and infant age group will depend on the number and severity of the nails affected, as well as the existence of other comorbid conditions.

Onycholysis

Separation of the nail plate from the nail bed is known as onycholysis. This usually occurs at the distal free edge of the nail plate, but may be observed laterally as well. The separation creates a narrow space that can fill with keratin, exogenous debris, or fluids such as water or saliva. The air pocket of the cleft gives an onycholytic nail a grayish-white color. Onycholysis is a physical sign for which there are numerous causes (Box 32.2).

Chromonychia

Nail dyschromia may be due to discoloration of the nail plate or nail bed (Table 32.2).⁸⁹ The causes of nail discoloration may be exogenous, secondary to local infectious agents, systemic drugs or diseases, primary skin diseases, or ungual neoplasms (Fig. 32.13). The shape of the discolored area depends upon how and where in the nail unit the pigment is deposited, and the duration of the pigment deposition.

TABLE
32.2

Chromonychia (nails with abnormal color)

Condition	Color	Other features
Hematomas	Purple	Observed on fingers, similar to sucking blisters (Fig. 32.13)
Endocarditis	Purple	Splinter-shaped
Phototoxicity	Purple	Drugs, porphyrias
Hyperbilirubinemia	Yellow-brown	Scleral icterus
Yellow nail syndrome	Yellow	Lymphedema, respiratory disease, nephrotic syndrome
Pernicious anemia	Blue-gray	Macrocytosis
Onychomycosis	Gray-green	<i>Aspergillus</i> , <i>Pseudomonas</i>
Candidiasis	White	
PCB exposure	Brown-gray	
Addison/Cushing disease	Brown	



Figure 32.13 A dusky violaceous hue of the nail beds resulting from ecchymoses and an eroded blister caused by vigorous intrauterine sucking.

Leukonychia (white nails) is the most common type of nail dyschromia.⁹⁰ It should not be confused with onycholysis. Total or subtotal leukonychia may be inherited as an autosomal dominant trait.⁹¹ Partial leukonychia on the distal portion of the nail apparatus may be a sign of congenital candidiasis limited to the nail plates.⁹² Proximal partial leukonychia is also a sign of subungual onychomycosis from dermatophytes or other fungi.⁹³ Transversely striated leukonychia in a longitudinal band may be observed after a febrile illness, similar to Beau's lines. Multiple striations are associated with successive events that affect the matrix, including the administration of chemotherapeutic agents,⁹⁴ the classic Mees' lines of heavy metal intoxication, or Muehrcke's paired lines of hypoalbuminemia. Muehrcke's lines have also been described in the presence of zinc deficiency. Partial leukonychia in which the proximal portion of the nail is white has several eponyms. They include Lindsay's half-and-half nails of uremia, and Terry's nails secondary to cirrhosis or congestive heart failure. Leukonychia may also be a sign of malnutrition or iron deficiency anemia. Punctate leukonychia is manifested by small, irregular white spots. It is usually caused by repeated minor trauma to the nail matrix.

Single longitudinal pigmented bands of the nail in children are due to melanocytic lesions located in the nail matrix



Figure 32.14 A longitudinal pigmented band of the nail plate develops from a nevocellular nevus in the nail matrix.

(Fig. 32.14).⁹⁵ Multiple longitudinal pigmented bands are common in dark-skinned persons but are unusual in children. Multiple brown bands may be observed in fetal hydantoin syndrome, Addison and Cushing disease, Peutz–Jeghers syndrome, HIV, and after exposure to maternal chlorpromazine ingestion

or other maternally ingested drugs.⁹⁶ A study of longitudinal pigmented bands in 100 individuals found that 22 had nail matrix nevi.⁹⁷ Twelve patients had lesions present at birth, and most were located on the fingernails. The bands were different shades, from light tan to black, and their width varied from 2 mm to the breadth of the entire nail plate. Periungual pigmentation (Hutchinson's sign) was present in many of these benign lesions. In a series of eight cases of longitudinal melanonychia in children, four were present at birth.⁹⁸ No cases of melanoma were documented in either series. There have even been isolated reports of spontaneous regression of ungual nevi.⁹⁹ To date, six cases of melanoma of the nail unit in young children have been reported.¹⁰⁰ Most cases of suspected ungual melanomas are probably benign Spitz nevi. Their pathology should be interpreted with caution, even by dermatopathologists. Most experts in nail diseases do not recommend biopsy of longitudinal pigmented bands unless a previously stable lesion undergoes progressive, rapid change. Biopsy specimens should be obtained from children who are predisposed to developing malignancies (e.g., xeroderma pigmentosum or dysplastic nevus syndrome). Improperly performed biopsies can lead to permanent nail dystrophy.

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KEY REFERENCES

72. Zac RI, Cafe ME, Neves DR, et al. Onychomycosis in a very young child. *Pediatr Dermatol* 2009;26:761–2.
76. Bonifaz A, Saul A, Mena C, et al. Dermatophyte onychomycosis in children under 2 years of age: experience of 16 cases. *J Eur Acad Dermatol Venereol* 2007;21:115–17.
77. Gupta AK, Skinner AR. Onychomycosis in children: a brief overview with treatment strategies. *Pediatr Dermatol* 2004;21:74–9.
78. Chun DK, Lee UH, Park HS, et al. Onychomycosis in a premature infant caused by *Candida tropicalis*. *J Eur Acad Dermatol Venereol* 2004;18:617–18.
80. Koklu E, Gunes T, Kurtoglu S, et al. Onychomycosis in a premature infant caused by *Candida parapsilosis*. *Pediatr Dermatol* 2007;24:155–6.
83. Sanchez-Schmidt JM, Vicente-Villa MA, Vinas-Arenas M, et al. Isolated congenital nail candidiasis: report of 6 cases. *Pediatr Infect Dis J* 2010;29:974–6.
84. Yamamoto T, Yokoyama A. Superficial white onychomycosis of the fingernails in a 1-year-old child with hypoxemia. *Pediatr Dermatol* 2007;24:95–6.
86. Hsu MM. Rapid response of distal subungual onychomycosis to 5% amorolfine nail lacquer in a 20-month-old healthy infant. *Pediatr Dermatol* 2006;23:410–11.
87. Sachdeva S, Gupta S, Prasher P, et al. *Trichophyton rubrum* onychomycosis in a 10-week-old infant. *Int J Dermatol* 2010;49:108–9.
88. Khurana VK, Gupta RK, Pant L, et al. *Trichophyton rubrum* onychomycosis in an 8-week-old infant. *Indian J Dermatol Venereol Leprol* 2011;77:625.

REFERENCES

- Baran R, Dawber RPR. Diseases of the nails and their management. 2nd ed. Oxford: Blackwell Scientific; 1994. p. 324–7.
- Silverman R, Baran R. Nail and appendageal abnormalities. In: Schachner LA, Hansen RC, editors. Pediatric dermatology. 3rd ed. Philadelphia: Elsevier; 2003. p. 574.
- Turano AF. Transverse nail ridging in early infancy. Pediatrics 1968;41:996–7.
- Wolf D, Wolf R, Goldberg MD. Beau's lines, a case report. Cutis 1982;29:191–4.
- Yinnon AM, Matalon M. Koilonychia of the toenails in children. Int J Dermatol 1988; 27:685–7.
- Nguyen V, Buka RL, Roberts B, et al. Koilonychia, dome-shaped epiphyses, and vertebral platyspondylia. J Pediatr 2005;147:112–14.
- Hogan GR, Jones B. The relationship of koilonychia and iron deficiency in infants. J Pediatr 1970;77:1054–7.
- Crosby DL, Petersen MJ. Familial koilonychia. Cutis 1989;44:209–10.
- Bumpers RD, Bishop ME. Familial koilonychia: a current case. Arch Dermatol 1980;116:845–6.
- Chapman RS. Overcurvature of the nails: an inherited disorder. Br J Dermatol 1973;89: 211–13.
- Egawa T. Congenital claw-like fingers and toes. Plast Reconstr Surg 1977;59:569–74.
- Takeshi M, Tadao K, Ogawa Y, et al. Claw nail deformity of the toe accompanied with cleft hand. J Plast Reconstr Surg 1998;101: 427–30.
- Iwasa M, Hirose T, Matsuo K. Congenital curved nail of the fourth toe. Plast Reconstr Surg 1991;553–4.
- Lin YC, Wu YH, Scher RK. Congenital curved nail of the fourth toe – three different clinical presentations. Pediatr Dermatol 2007;24:380–3.
- Johnson CF. Broad thumbs and broad great toes with facial abnormalities and mental retardation. Pediatrics 1966;68:942.
- Silverman RA. Nail and appendageal disorders. In: Schachner LA, Hansen RC, editors. Pediatric dermatology. 2nd ed. London: Churchill Livingstone; 1995. p. 629.
- Katz BZ. Finger clubbing as sign of HIV infection in children [letter]. Lancet 1997;349:575.
- Hopsu-Havu VK, Jansen CT. Anonychia congenita. Arch Dermatol 1973;107:752–3.
- Teebi AS, Kaurah P. Total anonychia congenita and microcephaly with normal intelligence: a new autosomal-recessive syndrome? Am J Med Genet 1996;66:257–60.
- Nevin NC, Thomas PS, Eady DJ, et al. Anonychia and absence/hypoplasia of distal phalanges (Cook's syndrome): report of a second family. J Med Genet 1995;32:638–41.
- Rahbari H, Heath L, Chapel TA. Anonychia with ectrodactyly. Arch Dermatol 1975;111: 1482–3.
- Verbov J. Anonychia with bizarre flexural pigmentation – an autosomal dominant dermatosis. Br J Dermatol 1975;92:469–74.
- Strandskov HH. Inheritance of absence of thumbnails. J Hered 1939;30:53–4.
- Robinson GC, Miller JR, Bensimon JR. Familial ectodermal dysplasia with sensorineural deafness and other anomalies. Pediatrics 1962; 30:797–802.
- Qazi QH, Heckman LS, Markouizos D, et al. The Coffin–Siris syndrome. J Med Genet 1990; 27:333–6.
- Seitz CS, Hamm H. Congenital brachydactyly and nail hypoplasia: clue to bone-dependent nail formation. Br J Dermatol 2005;152:1339–42.
- Bruckner-Tuderman L, Schnyder UW, Baran R. Nail changes in epidermolysis bullosa: clinical and pathogenic considerations. Br J Dermatol 1995;132:339–44.
- Crain LS, Fitzmaurice NE, Mondry C. Nail dysplasia and fetal alcohol syndrome. Am J Dis Child 1983;137:1069.
- D'Souza SW, Robertson IG, Donnai D. Fetal phenytoin exposure, hypoplastic nails, and jitteriness. Arch Dis Child 1990;65:320.
- Hsu MM, Mak CP, Hus CC. Follow-up of skin manifestations in Yu-Cheng children. Br J Dermatol 1995;132:427–32.
- Thakker JC, Kothari SS, Deshmukh KL, et al. Hypoplasia of nails and phalanges: a teratogenic manifestation of phenobarbitone. Indian Pediatr J 1991;28:73.
- Jäger-Roman E, Deichl A, Jakob S, et al. Fetal growth, major malformations, and minor anomalies in infants born to women receiving valproic acid. J Pediatr 1986;108:997.
- Duester GA. Hypothetical mechanism for fetal alcohol syndrome involving ethanol inhibition of retinoic acid synthesis at the alcohol dehydrogenase step. Alcohol Clin Exp Res 1991;15: 568–72.
- Fex G, Larsson K, Andersson A, et al. Low serum concentration of all-trans and 13-cis retinoic acids in patients treated with phenytoin, carbamazepine, and valproate: possible relation to teratogenicity. Arch Toxicol 1995; 69:572–4.
- Lucas GL, Opitz JM. The nail–patella syndrome: clinical and genetic aspects of 5 kindreds with 38 affected family members. J Pediatr 1966;68:273–88.
- Simila S, Vesä L, Wasz-Hockert O. Hereditary onycho-osteodysplasia (the nail–patella syndrome) with nephrosis-like renal disease in a newborn boy. Pediatrics 1970;46:61–5.
- Daniel CR III, Osment LS, Noojin RO. Triangular lunulae: a clue to nail–patella syndrome. Arch Dermatol 1980;116:448–9.
- Carbonara P, Kane AC, Alpert M. Hereditary osteo-onychodysplasia (HOOD). Am J Med Sci 1964;248:139–51.
- Browning MC, Weidner N, Lorentz WB Jr. Renal histopathology of the nail–patella syndrome in a two-year-old boy. Clin Nephrol 1988;29:210–13.
- Drut RM, Chandra S, Latorraca R, et al. Nail–patella syndrome in a spontaneously aborted 18-week fetus: ultrastructural and immunofluorescent study of the kidneys. Am J Med Genet 1992;43:693–6.
- Lichter PR, Richards JE, Downs CA, et al. Cosegregation of open-angle glaucoma and the nail–patella syndrome. Am J Ophthalmol 1997;124:506–15.
- Gilula LA, Kantor OS. Familial colon carcinoma in nail–patella syndrome. Am J Roentgenol 1975;123:783–90.
- Burkhardt CG, Bhumbra R, Iannone AM. Nail–patella syndrome: a distinctive clinical and electron microscopic presentation. J Am Acad Dermatol 1980;3:251–6.
- Dreyer SD, Zhou G, Baldini A, et al. Mutations in LMX1B cause abnormal skeletal patterning and renal dysplasia in nail patella syndrome. Nature Genet 1998;19:47–50.
- Greenspan DC, Byers MG, Eddy RL, et al. Human collagen gene COL5A1 maps to the q34.2 q34.3 region of chromosome 9, near the locus for nail–patella syndrome. Genomics 1992;12:836–7.
- Iso R. Congenital nail defects of the index finger and reconstructive surgery. Orthop Surg (Tokyo) 1969;20:1383–4.
- Baran R, Stroud JD. Congenital onychodysplasia of the index fingers. Iso and Kikuchi syndrome. Arch Dermatol 1984;120:243–4.
- Prais D, Horev G, Merlob P. Prevalence and new phenotypic and radiologic findings in congenital onychodysplasia of the index finger. Pediatr Dermatol 1999;16:201–4.
- Youn SH, Kwon OS, Park KC, et al. Congenital onychodysplasia of the index fingers – Iso–Kikuchi syndrome. A case involving the second toenail. Clin Exp Dermatol 1996;21:457–8.
- Kikuchi I. Congenital onychodysplasia of the index fingers: a case involving the thumbnails. Semin Dermatol 1991;10:7–11.
- Miura T, Nakamura R. Congenital onychodysplasia of the index fingers. J Hand Surg 1990;15A:793–7.
- Millman AJ, Strier RP. Congenital onychodysplasia of the index fingers. Report of a family. J Am Acad Dermatol 1982;7:57–65.
- Schmidt H. Total onychogryphosis traced during six generations. Proc Fenno Scand Assoc Dermatol 1965;36–7.
- Lubach D. Erbliche onychogryphosis. Hautarzt 1982;33:331.
- Leachman SA, Kaspar RL, Fleckman P, et al. Clinical and pathological features of pachyonychia congenita. J Invest Dermatol Symp Proc 2005;10:3–17.
- Baran R, Bureau H. Congenital malalignment of the big toenail as a cause of ingrowing toenail in infancy: pathology and treatment (a study of thirty cases). Clin Exp Dermatol 1983;8:619–23.
- Harper KJ, Beer WE. Congenital malalignment of the great toenails – an inherited condition. Clin Exp Dermatol 1986;11:514–16.
- Cohen JL, Scher RK, Pappert AS. Congenital malalignment of the great toenails. Pediatr Dermatol 1991;8:40–2.
- Dawson TA. Great toe-nail dystrophy. Br J Dermatol 1989;20:139.
- Baran R. Significance and management of congenital malalignment of the big toenail. Cutis 1996;58:181–4.
- Eliason MJ, Leachman SA, Feng BJ, et al. A review of the clinical phenotype of 254 patients with genetically confirmed pachyonychia congenita. J Am Acad Dermatol 2012;67(4): 680–6.
- Choi YH, Song CH, Lee JS, et al. Congenital malalignment of the fourth toenail with congenital curved nail of the contralateral fourth toe. Ann Dermatol 2013;25(1):133–4.
- Murray SC, Dawber RP, Khumalo N. Congenital malalignment of the left index fingernail. Br J Dermatol 2001;144(4):911–12.
- Hammerton MD, Shrank AB. Congenital hypertrophy of the lateral nailfolds of the hallux. Pediatr Dermatol 1988;5:243–5.
- Honig PJ, Spitzer A, Bernstein R, et al. Congenital ingrown toenails. Clin Pediatr 1982; 21:424–6.
- Baillie FB, Evans DM. Ingrowing toenails in infancy. BMJ 1978;2:737–8.

67. Ito T, Ito N, Saathoff M, et al. Immunology of the human nail apparatus: The nail matrix is a site of relative immune privilege. *J Invest Dermatol* 2005;125:1139–48.
68. Raval DS, Barton LL, Hansen RC, et al. Congenital cutaneous candidiasis: case report and review. *Pediatr Dermatol* 1995;12:355–8.
69. Sinniah D, Sandiford BR, Dugdale AE. Subungual infection in the newborn: an institutional outbreak of unknown etiology, possibly due to *Veillonella*. *Clin Pediatr* 1972;11:690–2.
70. De Berker D, Lever LR, Windebank K. Nail features in Langerhans cell histiocytosis. *Br J Dermatol* 1994;130:523–7.
71. Russo F, Collantes C, Guerrero J. Severe paronychia due to zidovudine-induced neutropenia in a neonate. *J Am Acad Dermatol* 1999;40:322–4.
72. Zac RI, Cafe ME, Neves DR, et al. Onychomycosis in a very young child. *Pediatr Dermatol* 2009;26:761–2.
73. Gupta AK, Sibbald RG, Lynde CW, et al. Onychomycosis in children: prevalence and treatment strategies. *J Am Acad Dermatol* 1997;36:395–402.
74. Kurgansky D, Sweren R. Onychomycosis in a 10-week-old infant. *Arch Dermatol* 1990;126:1371.
75. Reichert-Penetrat S, Contet-Audonnet N, Barbaud A, et al. Epidemiology of dermatophytoses in children living in northeast France: a 5-year study. *Pediatr Dermatol* 2002;19:103–5.
76. Bonifaz A, Saul A, Mena C, et al. Dermatophyte onychomycosis in children under 2 years of age: experience of 16 cases. *J Eur Acad Dermatol Venereol* 2007;21:115–17.
77. Gupta AK, Skinner AR. Onychomycosis in children: a brief overview with treatment strategies. *Pediatr Dermatol* 2004;21:74–9.
78. Chun DK, Lee UH, Park HS, et al. Onychomycosis in a premature infant caused by *Candida tropicalis*. *J Eur Acad Dermatol Venereol* 2004;18:617–18.
79. Sardana K, Garg VK, Manchanda V, et al. Congenital candidal onychomycosis: effective cure with ciclopirox olamine 8% nail lacquer. *Br J Dermatol* 2006;154:573–5.
80. Koklu E, Gunes T, Kurtoglu S, et al. Onychomycosis in a premature infant caused by *Candida parapsilosis*. *Pediatr Dermatol* 2007;24:155–6.
81. Clegg HW, Prose NS, Greenberg DN. Nail dystrophy in congenital cutaneous candidiasis. *Pediatr Dermatol* 2003;20:342–4.
82. Gibney MD, Siegfried EC. Cutaneous congenital candidiasis: a case report. *Pediatr Dermatol* 1995;12:359–63.
83. Sanchez-Schmidt JM, Vicente-Villa MA, Vinas-Arenas M, et al. Isolated congenital nail candidiasis: report of 6 cases. *Pediatr Infect Dis J* 2010;29:974–6.
84. Yamamoto T, Yokoyama A. Superficial white onychomycosis of the fingernails in a 1-year-old child with hypoxemia. *Pediatr Dermatol* 2007;24:95–6.
85. Patel NC, Silverman RA. Neonatal onychomadesis with candidiasis limited to affected nails. *Pediatr Dermatol* 2008;25:641–2.
86. Hsu MM. Rapid response of distal subungual onychomycosis to 5% amorolfine nail lacquer in a 20-month-old healthy infant. *Pediatr Dermatol* 2006;23:410–11.
87. Sachdeva S, Gupta S, Prasher P, et al. Trichophyton rubrum onychomycosis in a 10-week-old infant. *Int J Dermatol* 2010;49:108–9.
88. Khurana VK, Gupta RK, Pant L, et al. Trichophyton rubrum onychomycosis in an 8-week-old infant. *Indian J Dermatol Venereol Leprol* 2011;77:625.
89. Paradisis M, Van Asperen P. Yellow nail syndrome in infancy. *J Paediatr Child Health* 1997;33:454–7.
90. Zaun H. Leukonychia. *Semin Dermatol* 1991;10:17–20.
91. Stevens KR, Leis PF, Peters S, et al. Congenital leukonychia. *J Am Acad Dermatol* 1998;39:509–12.
92. Arbegast KD, Lamberty LF, Koh JK, et al. Congenital candidiasis limited to the nail plates. *Pediatr Dermatol* 1990;7:310–12.
93. Baran R, Tosti A, Piraccini BM. Uncommon clinical patterns of *Fusarium* nail infection: report of 3 cases. *Br J Dermatol* 1997;136:424–7.
94. Shelly WB, Humphrey GB. Transverse leukonychia (Mees' lines) due to daunorubicin chemotherapy. *Pediatr Dermatol* 1997;14:144–5.
95. Goettmann-Bonvallet S, André J, Belaich S. Longitudinal melanonychia in children: A clinical and histopathologic study of 40 cases. *J Am Acad Dermatol* 1999;41:17–22.
96. Silverman RA. Nail and appendageal abnormalities. In: Schachner LA, Hansen RD, editors. *Pediatric dermatology*. 2nd ed. New York: Churchill Livingstone; 1995. p. 635–6.
97. Tosti A, Baran R, Piraccini BM, et al. Nail matrix nevi: A clinical and histopathologic study of twenty-two patients. *J Am Acad Dermatol* 1996;34:765–71.
98. Léauté-Labreze C, Bioulac-Sage P, Taïeb A. Longitudinal melanonychia in children: a study of eight cases. *Arch Dermatol* 1996;132:167–9.
99. Tosti A, Baran R, Morelli R, et al. Progressive fading of a longitudinal melanonychia due to a nail matrix melanocytic nevus in a child. *Arch Dermatol* 1994;130:1076–7.
100. Antonovich DD, Grin C, Grant-Kels JM. Childhood subungual melanoma in situ in diffuse nail melanosis beginning as expanding longitudinal melanonychia. *Pediatr Dermatol* 2005;22:210–12.

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